ORIGINAL SUBMISSION

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NOTIFICATION OF GRAS DETERMINATION FOR SOY LECITHIN PHOSPHATIDYLSERINE COMPLEX

LIPOGEN PRODUCTS (9000) LTD.

NOVEMBER 29, 2005

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December 9, 2005

BY FAX and MAIL

Edmundo Garcia
Office of Premarket Approval (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: Notification of GRAS Determination for Soy Lecithin Phosphatidylserine Complex

Dear Mr. Garcia:

On behalf of Lipogen Products (9000) Ltd., we hereby submit this revised GRAS Exemption Claim. This page should replace the current GRAS Exemption Claim on the Notification already submitted.

Please contact me directly with any questions.

Sincerely,

Diane McEnroe

Encls.

SOY LECITHIN PHOSPHATIDYLSERINE COMPLEX NOTIFICATION

I. GRAS Exemption Claim

I-A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

The soy lecithin phosphatidylserine complex, which is derived through an enzymatic process using phospholipase D from cabbage, as defined in the report in Appendix I entitled, **"EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SOY LECITHIN PHOSPHATIDYLSERINE COMPLEX FOR USE IN FOODS"**, dated November, 2005 ([redacted]), has been determined to be Generally Recognized as Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in food, among experts qualified by scientific training and expertise. Therefore, the use of the soy lecithin phosphatidylserine complex in food as described below is exempt from the requirement of premarket approval.

Signed,

David Rutenberg
General Manager
Lipogen Products (9000) Ltd.

Nov. 16, 2005
Date

I-B. Name and Address of Notifier

David Rutenberg
General Manager
Lipogen Products (9000) Ltd.
60 Harofeh Street
P.O. Box 7687
Haifa
Israel, 31076

I-C. Common Name of the Notified Substance

Soy lecithin phosphatidylserine complex; soy lecithin PS complex

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I-D. Conditions of Intended Use in Food

Lipogen, Ltd. intends to market the soy lecithin phosphatidylserine complex as a food ingredient to provide a dietary source of phosphatidylserine. The individual proposed food-uses and use-levels for the complex are summarized in Table 1.

Table 1 Summary of the Individual Proposed Food-Uses and Use-Levels for Soy Lecithin Phosphatidylserine Complex in the United States

Food Category	Proposed Food-Use	Soy Lecithin Phosphatidylserine Complex/Serving Size	Soy Lecithin Phosphatidylserine Complex Use-Level (%)
Baked Goods and Baking Mixes	Breads and Rolls	50 mg/100 g to 25 mg/30 g	0.05 to 0.083
	Biscuits	25 mg/ 30 g	0.083
	Crackers	25 mg/ 30 g	0.083
	Waffles	50 mg/100 g	0.050
Beverages and Beverage Bases	Carbonated Beverages	100 mg/200 mL	0 050
	Meal Replacements (liquid)	100 mg/200 mL	0.050
Breakfast Cereals	Ready-to-Eat Breakfast Cereals	25 mg/30 g	0.083
Cheese	Cheese	25 mg/10 g	0.250
	Cheese Spreads	25 mg/10 g	0.250
Coffee and Tea	Coffee	100 mg/200 mL	0.050
	Tea	100 mg/200 mL	0.050
Condiments and Relishes	Ketchup	25 mg/5 g	0.500
Dairy Product Analogs	Soy-Based Milk	100 mg/200 mL	0.050
Fats and Oils	Margarine	25 mg/10 g	0.250
	Mayonnaise and Mayonnaise-Type Dressing	25 mg/5 g	0.500
	Fat-Based Spreads	25 mg/10 g	0.250
Grain Products and Pastas	Pasta	50 mg/100 g	0.050
	Grain-Based Bars	50 mg/100 g	0.050
Jams and Jellies	Commercial Jams	25 mg/10 g	0.250
Milk	Milk	100 mg/200 mL	0.050
Milk Products	Milk Drinks	100 mg/200 mL	0.050
	Yogurt	100 mg/200 mL	0.050
Nut and Nut products	Peanut Spreads	25 mg/10 g	0.250
Plant Protein Products	Tofu	25 mg/10 g	0.250
	Soy-Based Meat Substitutes	100 mg/200 g	0.050

Table 1 Summary of the Individual Proposed Food-Uses and Use-Levels for Soy Lecithin Phosphatidylserine Complex in the United States

Food Category	Proposed Food-Use	Soy Lecithin Phosphatidylserine Complex/Serving Size	Soy Lecithin Phosphatidylserine Complex Use-Level (%)
Processed Fruits and Fruit Juices	Fruit Juices	100 mg/200 mL	0.050
Snack Foods	Salty Snacks	100 mg/200 g	0.050
Soft Candy	Chocolates	100 mg/200 g	0.050

The soy lecithin phosphatidylserine complex is a mixture of naturally occurring soy lecithin phospholipids enriched *via* enzymatic modification in phosphatidylserine. Phosphatidylserine is an essential structural component of plant and animal cell membranes and is a naturally occurring constituent of the human diet. Apart from bovine brain, which has the highest levels of phosphatidylserine, fish, specifically mackerel, herring and eel, as well as white beans also are rich sources of naturally occurring phosphatidylserine (Souci *et al.*, 2000). Phosphatidylserine also is secreted in human breast milk, and thus it is thought to function in the development of a newborn's brain (Harzer *et al.*, 1983). Based on unpublished sources, the daily intake of phosphatidylserine from a typically varied Western diet is estimated to be approximately 130 mg/day; however, a diet rich in meat and/or fish can provide up to 180 mg of phosphatidylserine/day. Daily intake of phosphatidylserine from 200 g of bovine skeletal muscle alone is calculated to provide 80 mg phosphatidylserine/day (0.1 mmol phosphatidylserine/day) (Bruni *et al.*, 1992).

The consumption of soy lecithin phosphatidylserine complex from all proposed food-uses was estimated using the USDA 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996) and the 1998 Supplemental Children's Survey (USDA CSFII 1998) (USDA, 2000). Depending on the particular food category, the complex is proposed for use as a food ingredient at levels providing between 0.05 to 0.5%. The estimated daily consumption of the complex from all proposed food-uses at the proposed use-levels per serving was calculated on a g and mg per kilogram body weight basis by population group.

On an all-user basis, the mean and 90th percentile intakes of the soy lecithin phosphatidylserine complex by the total U.S. population from all proposed food-uses were estimated to be 0.71 g/person/day (12.8 mg/kg body weight/day) and 1.19 g/person/day (23.5 mg/kg body weight/day), respectively. Based on the composition of the complex of approximately 20% phosphatidylserine, these estimates result in mean and heavy consumer intakes of approximately 140 mg/person/day (2.6 mg/kg body weight/day) and 240 mg/person/day (4.7 mg/kg body weight/day). On an absolute basis, male teenagers were identified to have the highest man and 90th percentile all-user intakes of the complex (0.87 and 1.44 and g/person/day, respectively),

while infants were estimated to have the greatest mean and 90th percentile all-user intakes of the complex on a body weight basis (31.4 and 55.3 mg/kg body weight/day, respectively).

I-E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, the soy lecithin phosphatidylserine complex has been determined to be GRAS on the basis of scientific procedures (see Appendix I entitled, **"EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SOY LECITHIN PHOSPHATIDYLSERINE COMPLEX FOR USE IN FOODS"**.

I-F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Diane McEnroe
Sidley Austin Brown & Wood LLP
787 Seventh Avenue
New York, New York 10019

Should the FDA have any questions or additional information requests regarding this notification, Sidley Austin Brown & Wood will supply these data and information.

II. Detailed Information About the Identity of the Substance

II-A. Identity

Lipogen's soy lecithin phosphatidylserine complex is characterized by a phosphatidylserine composition of approximately 20%. Additionally, the soy lecithin-derived complex consists of several other phospholipids and glycerides indigenous to soy lecithin, an ingredient considered GRAS by the FDA. The soy lecithin phosphatidylserine complex formulations (powder and liquid) are composed of the ingredients listed in Table 2.

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Table 2 Ingredient Composition of the Powder and Liquid Soy Lecithin Phosphatidylserine Complexes

Ingredient	Powder	Liquid	FDA Regulatory Status
Phosphatidylserine and *lysophosphatidylserine*	Not less than 19%	Not less than 19%	GRAS status to be determined
Other phospholipids[1] and glycerides occurring naturally in soy lecithin	Not more than 81%	Not more than 63%	Soy lecithin is GRAS (21 CFR §184.1400)
Vitamin C	Not more than 2%	Not more than 1%	GRAS (21 CFR §182.3013, §182.8013)
Silicone dioxide	Not more than 1%	N/A	GRAS (21 CFR §172.480)
Soy oil	N/A	Not more than 19%	GRAS

N/A = Not applicable

[1] Including phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), and phosphatidylinositol (PI) and *lyso*-phospholipids.

Phospholipids are fat derivatives consisting of 2 fatty acids attached to a glycerol molecule to form phosphatidic acid. Depending on the formulation type (liquid or powder), fatty acids constitute between approximately 60 and 70% of the final Lipogen powder and liquid soy lecithin phosphatidylserine products. At least 50% of the total fatty acid composition of the soy lecithin phosphatidylserine complexes is characterized by the polyunsaturated fatty acid, linoleic acid. α-Linolenic acid, oleic acid, stearic acid, and palmitic acid comprise the remainder of the fatty acids of the soy lecithin phosphatidylserine complexes. The fatty acid composition of the soy lecithin phosphatidylserine complex is essentially identical to that of the soy lecithin raw material. Consequently, while soy lecithin-derived phosphatidylserine is characterized by a high polyunsaturated fatty acid content [*i.e.*, linoleic acid (ω-6; 18:2) and α-linolenic acid (ω-3; 18:3)], phosphatidylserine derived from mammalian brain consists mainly of saturated [*e.g.*, stearic acid (18:0)] and monounsaturated [*e.g.*, oleic acid (18:1)] fatty acids, as well as smaller amounts of long-chain polyunsaturated fatty acids, particularly docosahexaenoic acid (DHA) (ω-3; 22:6) and arachidonic acid (ω-6; 20:4) (Baer and Maurukas, 1955; Salem *et al.*, 1980; Blokland *et al.*, 1999; PDRNS, 2001; Mozzi *et al.*, 2003). The fatty acid composition of phosphatidylserine is a distinguishing factor between phosphatidylserine derived from soy lecithin or extracted from bovine brain (PDRNS, 2001; Mozzi *et al.*, 2003). Otherwise, phosphatidylserine obtained from either source is identical.

Phosphatidylserine and phosphatidylethanolamine are considered to be the main phospholipids of the brain (PDRNS, 2001). Endogenous production of phosphatidylserine occurs *via* direct conjugation of phosphatidic acid with serine or alternatively replacement of the ethanolamine moiety of phosphatidylethanolamine with serine. The structural formula and chemical properties of phosphatidylserine, as well as physical characteristics of the complexes are presented below.

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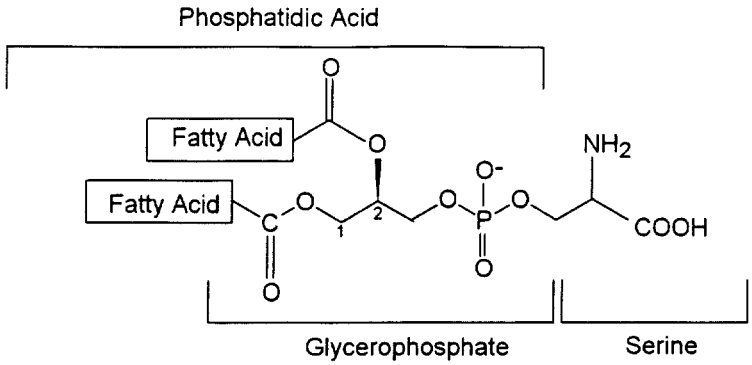
Structure:

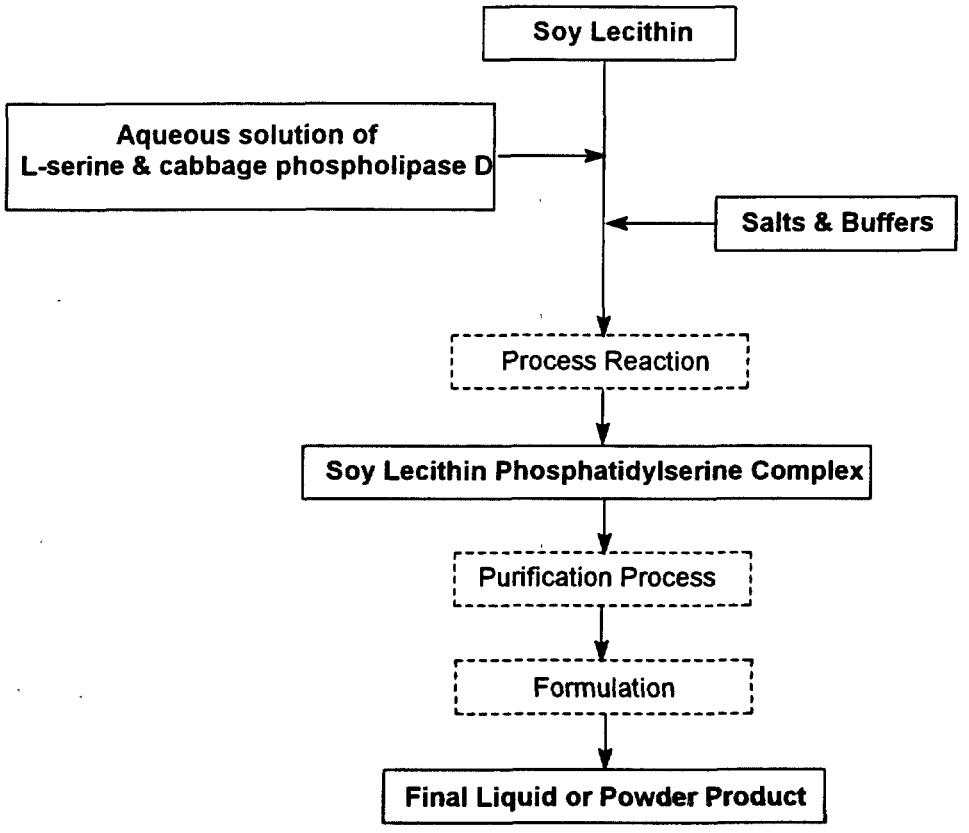


Synonyms:	1,2-Diacyl-*sn*glycerol-(3)-L-phosphoserine (also commonly abbreviated to Ptd Ser, $Acyl_2$ Gro Pser, and PS).
CAS Number:	[84776-79-4]
Empirical Formula:	Variable, depending on the composition of fatty acids.
Molecular Weight:	Same as above.
Appearance:	The soy lecithin phosphatidylserine complex is formulated into either a yellow-brown, fine granular powder or a brown liquid.
Solubility:	Both formulations are highly soluble in ether.

II-B. Method of Manufacture

In the past, phosphatidylserine was predominantly obtained from bovine brain extract; however, due to the potential for transmission of bovine prion infections (*e.g.*, spongiform encephalopathy), soy-derived phosphatidylserine has increasingly become another major source of commercially available phosphatidylserine for use by humans (Thorne Research Inc., 1999; PDRNS, 2001). The phosphatidylserine complex manufactured by Lipogen is derived from soy lecithin, and consists of serine-substituted soy lecithin phospholipids and other phospholipids occurring naturally in lecithin. With minor modification, production of Lipogen's soy lecithin phosphatidylserine complex follows that outlined in Ebil and Kovatchev (1981) and essentially involves the enzymatic transphosphatidylation of phosphatidylcholine and phosphatidylethanolamine from soy lecithin *via* cabbage-derived phospholipase D in the presence of exogenous serine to phosphatidylserine. Production of the phosphatidylserine-enriched complex proceeds without the use of any solvents at any stage during the manufacturing process, and thus the final soy lecithin phosphatidylserine complex is solvent-free. The product is manufactured in accordance with good manufacturing practice (GMP) and all raw materials involved in the manufacturing process are appropriate for food use. A schematic overview of the manufacturing process of the soy lecithin phosphatidylserine is provided in Figure 1. It should be noted that for the liquid product a higher yield of phosphatidylserine is produced prior to adding the soy oil so that the final liquid product also contains 19% phosphatidylserine.

Figure 1 **Schematic Overview of the Manufacturing Process for Soy Lecithin Phosphatidylserine Complex**



II-C. Specifications for Food Grade Material

The chemical, physical, and microbiological specifications for the soy lecithin phosphatidylserine complex are presented in Table 3. Analysis of nonconsecutive representative lots demonstrated compliance with final product chemical, physical and microbiological specifications, and stability under recommended storage conditions.

Table 3 Physical and Chemical Specifications for Soy Lecithin Phosphatidylserine Complexes

Specification Parameter	Specification	
	Powder	**Liquid**[1]
Appearance	Yellow-brown, fine granular powder	Brown liquid
Solubility	Dissolved in ether, solution is clear	Dissolved in ether, solution is clear
Identification (HPTLC separation of phospholipids)	Passes	Passes
Viscosity	N/A	Not more than 5,000 cps (at 30°C)
Phosphatidylserine and *lyso*phosphatidylserine (HPTLC)	Not less than 19%[2]	Not less than 19%[2]
Other phospholipids[3] and glycerides	Not more than 81%	Not more than 63%
Loss on Drying	Not more than 5%	Not more than 1%
Lead	<1 ppm	<1 ppm
Microbiological Specifications		
Total plate count	Not more than 1,000 CFU	Not more than 1,000 CFU
Yeast	Not more than 100 CFU	Not more than 100 CFU
Mould	Not more than 100 CFU	Not more than 100 CFU
Fecal Streptococci	Less than 10	Less than 10
Coliforms	Less than 10	Less than 10
Fecal Coliforms	Absent	Absent
Escherichia coli	Absent	Absent
Staphylococcus aureus	Absent	Absent
Salmonella	Absent	Absent

N/A = Not applicable; CFU = Colony forming unit;
[1] Product diluted with soy oil in amounts of 35 kg per 185 kg batch (19%).
[2] *lyso*Phosphatidylserine comprises not more than 5%.
[3] Including phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), and phosphatidylinositol (PI) and *lyso*-phospholipids.

III. Basis for GRAS Determination

Pursuant to 21 CFR §170.30, the soy lecithin phosphatidylserine complex intended for use by Lipogen Inc., as defined in Appendix I, has been determined to be GRAS on the basis of scientific procedures. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of the complex as a component of food. The safety of the soy lecithin phosphatidylserine complex is supported by an extensive number of published studies on this and similar complexes as well as on phosphatidylserine itself. Data pertaining to safety including metabolic studies, *in vitro* and *in vivo* mutagenicity/genotoxicity studies, acute, subchronic and chronic toxicity studies, and reproductive and developmental toxicity studies performed in various experimental animals, as well as numerous human clinical trials, which were primarily designed to investigate the potential for a beneficial association between an increased intake in phosphatidylserine and improvement in cognitive function in

elderly subjects. This determination is further supported by an Expert Panel evaluation of the safety of the soy lecithin phosphatidylserine complex (see Appendix I entitled, **"EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SOY LECITHIN PHOSPHATIDYLSERINE COMPLEX FOR USE IN FOODS"**).

The assessment of the safety of the soy lecithin phosphatidylserine complex included an extensive review of the metabolic fate of phosphatidylserine following oral consumption. Prior to absorption, phosphatidylserine has been demonstrated to be subject to phospholipase A_2-mediated hydrolysis to form *lyso*phosphatidylserine. In the intestinal absorptive cells, the monoacyl derivatives may be reacylated to phosphatidylserine with different fatty acids, and subsequently the serine moiety decarboxylated in exchange for ethanolamine to form phosphatidylethanolamine. Absorbed phospholipids are incorporated into lipoproteins and released into the circulation. Furthermore, the safety of the soy lecithin phosphatidylserine complex was assessed following review of a series of short- and long-term animal toxicity studies and *in vitro* and *in vivo* mutagenicity/genotoxicity assays conducted by Heywood *et al.*, (1987). Although the phosphatidylserine test material used in these studies was obtained from bovine brain tissue, as previously noted differences in phosphatidylserine from the two sources are limited only to the fatty acids composition. While brain-derived phospholipids are characterized by the presence of DHA, phospholipids from soy will contain larger proportions of linoleic acid and α-linolenic acid. Both linoleic acid and α-linolenic acid are essential fatty acids, with α-linolenic acid being a precursor of DHA. Moreover, the fatty acid composition of differently sourced phospholipids is not firmly set, but is rather a distribution of fatty acids, with some occurring in greater amounts than others depending on the source. As such there is an overlap in the fatty acids profile of phosphatidylserine extracted from soy and bovine brain. Prior to absorption, phosphatidylserine is subjected to enzymatic activity, which results in the cleavage of the fatty acids. The resulting *lyso* metabolites, as well as free fatty acids are expected to be similarly processed by the body. Ultimately, reacylated phosphatidylserine may be converted to phosphatidylethanolamine, which is considered to be the predominant phospholipid of mammalian cells. However, the reattached acyl group may not necessarily be the same fatty acid as that which was initially cleaved off. Such remodeling of the acyl groups as a result of phospholipase A_2, as well as phospholipase A_1 activity, continues to occur as the phospholids circulate following absorption as part of chylomicrons. Therefore, the fatty acid makeup of the absorbed phosphatidylserine may be considerably changed from that of the administered phosphatidylserine and will largely depend on the fatty acids available in the specific tissues in which the conversion is taking place. As such, the differences in the fatty acid profile of exogenously administered phosphatidylserine are not expected to affect the safety of phosphatidylserine following oral consumption.

With respect to the overall safety of the soy lecithin phosphatidylserine complex, it should be emphasized that the raw material soy lecithin has been affirmed as GRAS by the FDA. Accordingly, with the exception of the phosphatidylserine component of the complex and more specifically the serine since the phosphatidic acid backbone is that of the phospholipids present

in the soy lecithin raw material, the remaining constituents of the complex are common to the composition of the raw material. Nonetheless, a number of human clinical efficacy and safety trials were identified, which were performed with soy lecithin phosphatidylserine complexes, including several published and unpublished trials with Lipogen's product. Additionally, human data indicating no adverse effects following consumption of bovine-brain-derived phosphatidylserine in a number of efficacy trials further support the safety of the phosphatidylserine complex. The washing steps of the manufacturing process ensure that the final product does not contain any detectable levels of residual serine and is free of the cabbage juice extract, which is used as the source of phospholipase D.

Evaluation by the Expert Panel of the scientific evidence pertaining to the safety of the soy lecithin phosphatidylserine complex under the intended conditions of use in foods resulted in the conclusion that the complex, "meeting appropriate food grade specifications, is Generally Recognized as Safe (GRAS) based on scientific procedures under the intended conditions of use specified herein" (see Appendix I).

IV. References

Baer, E.; Maurukas, J. 1955. Phosphatidyl serine. J Biol Chem 212:25-38.

Blokland, A.; Honig, W.; Brouns, F.; Jolles, J. 1999. Cognition-Enhancing properties of subchronic phosphatidylserine (PS) treatment in middle-aged rats: comparison of bovine cortex PS with egg PS and soybean PS. Nutrition 15(10):778-783.

Bruni, A.; Orlando, P.; Mietto, L.; Viola, G. 1992. Phospholipid metabolism in rat intestinal mucosa after oral administration of lysophospholipids. In: Bazan, N.G. (Ed.) Neurobiology of Essential Fatty Acids. New York: Plenum Press, 243-249.

Ebil, A.; Kovatchev, S. 1981. Preparation of phospholipids and their analogs by phospholipase D. Methods Enzymol 72:632-639.

Harzer, G.; Haug, M; Dieterich, I.; Gentner, P.R.; 1983. Changing patterns of human milk lipids in the course of the lactation and during the day. Am J Clin Nutr 37:612-621.

Heywood, R.; Cozens, D.D.; Richold, M. 1987. Toxicology of a phosphatidylserine preparation from bovine brain (BC-PS). Clin Trials J 24(1):25-32.

Mozzi, R.; Buratta, S.; Goracci, G. 2003. Metabolism and functions of phosphatidylserine in mammalian brain. Neurochem Res 28(2):195-214.

PDRNS. 2001. Phosphatidylserine. In: PDR For Nutritional Supplements (1st Ed.). Physicians' Desk Reference (PDR); Des Moines, Iowa/Medical Economics Data Production Company; Montvale, New Jersey. Available from: http://www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/pho_0202.shtml.

Salem, N. (Jr.); Serpentino, P.; Puskin, J.S.; Abood, L.G. 1980. Preparation and spectroscopic characterization of molecular species of brain phosphatidylserine. Chem Phys Lipids 27:289-304.

Souci, S.W.; Fachmann, E.; Kraut, H. (Founders); Scherz, H.; Senser, F. (Compilers). 2000. [Content of phosphatidylserine in: Beans, Beef, Eggs, Eel, Herring, Poultry, Mackrel, Milk]. In: Food Composition and Nutrition Tables = Die Zusammensetzung der Lebensmittel Nährwert-Tabellen = La Composition des Aliments, Tableaux des Valeurs Nutritives (6th Rev. Compl. Ed. Ed.). CRC Press / Medpharm Scientific Publishers; Boca Raton / Stuttgart.

Thorne Research Inc. 1999. Monograph: Phosphatidylserine. Altern Med Rev 4(2):115-1417.

USDA. 2000. 1994-1996, 1998 Continuing Survey of Food Intakes by Individuals (CSFII) and Diet and Health Knowledge Survey (DHKS) (On CD-ROM). U.S. Department of Agriculture (USDA); Riverdale, Maryland. [PB2000-500027].

EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SOY LECITHIN PHOSPHATIDYLSERINE COMPLEX FOR USE IN FOODS

November, 2005

INTRODUCTION

At the request of Lipogen Products (9000) Ltd. (hereafter Lipogen), an Expert Panel (the "Panel") of independent scientists, qualified by their relevant national and international experience and scientific training, was specially convened on June 03, 2005 to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether, under the conditions of intended use as a food ingredient, soy lecithin phosphatidylserine complex in both powder and liquid formulations would be Generally Recognized as Safe (GRAS), based on scientific procedures. The data were revisited again in November 2005, prior to FDA notification. The Panel consisted of the below-signed qualified scientific experts: John Doull, Ph.D., M.D. (University of Kansas Medical Center), Earle R. Nestmann, Ph.D. (CANTOX Health Sciences International), and Gary M. Williams, M.D. (New York Medical College). *Curricula vitae* evidencing the Panel members' qualifications for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel, independently and collectively, critically examined a comprehensive package of publicly available scientific information and data compiled from the literature and other published sources through September 2005. In addition, the Panel evaluated other information deemed appropriate or necessary, including data and information provided by Lipogen. The data evaluated by the Panel included information pertaining to the method of manufacture and product specifications, analytical data, intended use levels in specified food products, consumption estimates for all intended uses, and comprehensive literature on the safety of soy lecithin phosphatidylserine complex.

Following independent, critical evaluation of such data and information, the Panel unanimously concluded that under the conditions of intended use in traditional foods described herein, Lipogen's soy lecithin phosphatidylserine complex, meeting appropriate food-grade specifications, and manufactured and used in accordance with current good manufacturing practices (GMPs), is GRAS based on scientific procedures. A summary of the basis for the Panel's conclusion, excluding confidential data and information, is provided below.

COMPOSITION AND FORMULATION

Commercial phosphatidylserine has been historically obtained from two sources, namely (1) bovine brain extract or, (2) *via* enzymatic conversion of other phospholipids, including

phosphatidylcholine or phosphatidylethanolamine. Given current concerns over bovine spongiform encephalitis, bovine derived phosphatidylserine has become less desirable. The phosphatidylserine comprising the phosphatidylserine complex manufactured by Lipogen is derived *via* serine-substitution of other phospholipids present in soy lecithin.

Lipogen's soy lecithin phosphatidylserine powder and liquid complexes contain several other phospholipids in addition to phosphatidylserine. These phospholipids occur naturally in soy lecithin, an ingredient considered by the U.S. Food and Drug Administration (FDA) to be GRAS. The soy lecithin phosphatidylserine complex formulations (powder and liquid) are composed of the ingredients listed in Table 1.

Table 1 Ingredient Composition of the Powder and Liquid Soy Lecithin Phosphatidylserine Complexes

Ingredient	Powder	Liquid	FDA Regulatory Status
Phosphatidylserine and *lyso*phosphatidylserine	Not less than 19%	Not less than 19%	Determined to be GRAS by Lipogen
Other phospholipids[1] and glycerides occurring naturally in soy lecithin	Not more than 81%	Not more than 63%	Soy lecithin is GRAS (21 CFR §184.1400)
Vitamin C	Not more than 2%	Not more than 1%	GRAS (21 CFR §182.3013, §182.8013)
Silicone dioxide	Not more than 1%	N/A	FDA approved direct food additive (21 CFR §172.480)
Soy oil	N/A	Not more than 19%	History of use

N/A = Not applicable

[1] Including phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), and phosphatidylinositol (PI) and *lyso*-phospholipids.

It should be noted that for the liquid product a higher yield of phosphatidylserine is obtained prior to adding the soy oil so that the final liquid product also contains 19% phosphatidylserine.

Phosphatidylserine consists of a glycerophosphate skeleton conjugated on one end with 2 fatty acids to form a phosphatidic acid backbone, and the amino acid L-serine, on the other end *via* a phosphodiester linkage (PDRNS, 2001). In total, fatty acids constitute approximately 76 and 62% of the final powder and liquid products, respectively. The polyunsaturated fatty acid, linoleic acid (*i.e.*, 9,12-octadecadienoic acid), comprises at least 50% of the total fatty acid composition of the soy lecithin phosphatidylserine powder and liquid complexes. Other fatty acids, including α-linolenic acid, oleic acid, stearic acid, and palmitic acid are found in smaller amounts. In comparison, mainly saturated and monounsaturated fatty acids, as well as the long-chain polyunsaturated fatty acid docosahexaenoic acid (DHA), constitute the fatty acid component of the phosphatidylserine derived from the bovine brain. Nevertheless, prior to absorption, both the phosphatidylserine from bovine or soy-derived sources would be cleaved from the fatty acid and be processed similarly by the body and consequently, no biological differences would be expected.

MANUFACTURING AND SPECIFICATIONS

Production of Lipogen's soy lecithin phosphatidylserine complex involves the enzymatic transphosphatidylation of phosphatidylcholine and phosphatidylethanolamine from soy lecithin *via* cabbage-derived phospholipase D in the presence of exogenous serine to phosphatidylserine. Phospholipase D [EC 3.1.4.4] is obtained *via* a water-based extraction from cabbage, which given its history of use is GRAS. Phospholipase D is a constituent of cabbage and therefore the enzyme is not expected to be a safety concern when used in the manufacture of phosphatidylserine from soy-derived phosphatidylcholine. Moreover, following the enzymatic conversion of phosphatidylcholine to phosphatidylserine, the reaction is terminated by bringing the reaction mixture to a temperature of 70°C. This temperature inactivates the enzyme, which is expected to denature as a result of the increasing temperatures. Any residue is removed as a result of the washing procedure.

All raw materials used in the manufacture of the phosphatidylserine complex (liquid or powder) are food grade as per the specifications presented in the Food Chemicals Codex (FCC). The product is manufactured in accordance with GMPs and does not involve use of any chemical solvents. Specifications for the soy lecithin phosphatidylserine complexes are presented in Table 2. Analyses of representative, non-consecutive lots of both the powder and liquid formulations consistently demonstrated compliance with final product specifications. It is expected that any residues (*e.g.*, serine) remaining in the complex following the enzymatic conversion are removed during the washing-processing step. In fact, analysis of the final product confirmed absence of serine at levels of detection. The formulation aids, silicone dioxide and vitamin C, are added to the final products at levels consistent with those permitted for use in food by the U.S. FDA (CFR, 2005). Additionally, analysis also was performed to ensure that the final products are free of pesticide contamination. In an assessment of product stability, conformity with product specifications was demonstrated following a 2-year storage period.

Table 2 Product Specifications for Soy Lecithin Phosphatidylserine Complex

Specification Parameter	Specification	
	Powder	Liquid[1]
Appearance	Yellow-brown, fine granular powder	Brown liquid
Solubility	Dissolved in ether, solution is clear	Dissolved in ether, solution is clear
Identification (HPTLC separation of phospholipids)	Passes	Passes
Viscosity	N/A	Not more than 5,000 cps (at 30°C)
Phosphatidylserine and *lyso*phosphatidylserine (HPTLC)	Not less than 19%[2]	Not less than 19%[2]
Other phospholipids[3] and glycerides	Not more than 81%	Not more than 63%

Table 2 Product Specifications for Soy Lecithin Phosphatidylserine Complex		
Specification Parameter	**Specification**	
	Powder	**Liquid**[1]
Loss on Drying	Not more than 5%	Not more than 1%
Lead	< 1 ppm	< 1 ppm
Microbiological Specifications		
Total plate count	Not more than 1,000 CFU	Not more than 1,000 CFU
Yeast	Not more than 100 CFU	Not more than 100 CFU
Mould	Not more than 100 CFU	Not more than 100 CFU
Fecal Streptococci	Less than 10	Less than 10
Coliforms	Less than 10	Less than 10
Fecal Coliforms	Absent	Absent
Escherichia coli	Absent	Absent
Staphylococcus aureus	Absent	Absent
Salmonella	Absent	Absent

N/A = Not applicable; HPTLC = High performance thin layer chromatography.
[1] Product diluted with soy oil in amounts of 35 kg per 185 kg batch (19%).
[2] *lyso*Phosphatidylserine comprises not more than 5%.
[3] Including phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), and phosphatidylinositol (PI) and *lyso*-phospholipids.

INTENDED USE AND ESTIMATED EXPOSURE

Phosphatidylserine is a necessary structural component of plant and animal cell membranes and is a constituent of the human diet occurring in foods such as soy products, eggs, and meats. In addition to bovine brain, which has the highest levels of phosphatidylserine, fish, particularly mackerel, herring, and eel, have been identified as primary sources of naturally occurring dietary phosphatidylserine (*i.e.*, 335 to 480 mg phosphatidylserine/100 g food) (Souci *et al.*, 2000). White beans also are a rich dietary source of phosphatidylserine. Based on the consumption of 200 g of bovine skeletal muscle per day, a daily intake level of phosphatidylserine from the diet is estimated at approximately 80 mg (0.1 mmol phosphatidylserine/day) (Bruni *et al.*, 1992). Phosphatidylserine is also present in human breast milk and is thought to function in the development of the newborn's brain (Harzer *et al.*, 1983).

Presently, enzyme-modified soy lecithin using phospholipase D is not added to food in the United States; however, unmodified soy lecithin, as well as phospholipase A_2- or pancreatin-modified lecithin, is considered GRAS in the United States and is approved for use in food with no limits other than current good manufacturing practice (CFR, 2005). It is also worth noting that soy lecithin phosphatidylserine complexes have been marketed in the U.S. since 1995 as dietary supplements under the *Dietary Supplement Health and Education Act of 1994* (DSHEA). Moreover, in 2003 the FDA approved a qualified health claim for phosphatidylserine complexes,

including highly purified phosphatidylserine derived from soy lecithin, related to their use as dietary supplements to reduce the risk of cognitive dysfunction and dementia (FDA, 2003, 2004). Typical daily dosages of phosphatidylserine as a dietary supplement are reported as 100 mg, 3 times per day for a total of 300 mg of phosphatidylserine, supplied as capsules (PDRNS, 2001). Furthermore, in Israel, Lipogen's soy lecithin phosphatidylserine complex has been marketed under the brand name L-Telect for more than 11 years. No side effects or any adverse events related to the consumption of the complex have been reported.

Lipogen intends to market the soy lecithin phosphatidylserine complex as a food ingredient in the US to provide a source of phosphatidylserine in a variety of food products including baked goods, beverages, cereals, cheese, coffee, tea, condiments, fats, oils, jams, milk, dairy product analogs, processed fruits and fruit juices, snack foods, soft candy, and grain, nut, plant protein and milk products. The individual proposed food-uses and use-levels for soy lecithin phosphatidylserine complex are summarized in Table 3. Depending on the particular food category, the soy lecithin phosphatidylserine complex is proposed for use as a food ingredient at use levels of up to 0.50% per serving. Food codes representative of each proposed food-use were chosen from the CSFII 1994-1996, 1998 (USDA, 2000) and grouped in food-use categories according to Title 21, Section §170.3 of the Code of Federal Regulations (CFR, 2003).

Table 3 Summary of the Individual Proposed Food-Uses and Use-Levels for Soy Lecithin Phosphatidylserine Complex in the United States

Food Category	Proposed Food-Use	Soy Lecithin Phosphatidylserine Complex/Serving Size	Soy Lecithin Phosphatidylserine Complex Use-Level (%)
Baked Goods and Baking Mixes	Breads and Rolls	50 mg/100 gram (g) to 25mg/30 g	0.05 to 0.083
	Biscuits	25 mg/ 30 g	0.083
	Crackers	25 mg/ 30 g	0.083
	Waffles	50 mg/100 g	0.050
Beverages and Beverage Bases	Carbonated Beverages	100 mg/200 mL	0.050
	Meal Replacements (liquid)	100 mg/200 mL	0.050
Breakfast Cereals	Ready-to-Eat Breakfast Cereals	25 mg/30 g	0.083
Cheese	Cheese	25 mg/10 g	0.250
	Cheese Spreads	25 mg/10 g	0.250
Coffee and Tea	Coffee	100 mg/200 mL	0.050
	Tea	100 mg/200 mL	0.050
Condiments and Relishes	Ketchup	25 mg/5 g	0.500
Dairy Product Analogs	Soy-Based Milk	100 mg/200 mL	0.050
Fats and Oils	Margarine	25 mg/10 g	0.250

Table 3 Summary of the Individual Proposed Food-Uses and Use-Levels for Soy Lecithin Phosphatidylserine Complex in the United States			
Food Category	**Proposed Food-Use**	**Soy Lecithin Phosphatidylserine Complex/Serving Size**	**Soy Lecithin Phosphatidylserine Complex Use-Level (%)**
	Mayonnaise and Mayonnaise-Type Dressing	25 mg/5 g	0.500
	Fat-Based Spreads	25 mg/10 g	0.250
Grain Products and Pastas	Pasta	50 mg/100 g	0.050
	Grain-Based Bars	50 mg/100 g	0.050
Jams and Jellies	Commercial Jams	25 mg/10 g	0.250
Milk	Milk	100 mg/200 mL	0.050
Milk Products	Milk Drinks	100 mg/200 mL	0.050
	Yogurt	100 mg/200 mL	0.050
Nut and Nut products	Peanut Spreads	25 mg/10 g	0.250
Plant Protein Products	Tofu	25 mg/10 g	0.250
	Soy-Based Meat Substitutes	100 mg/200 g	0.050
Processed Fruits and Fruit Juices	Fruit Juices	100 mg/200 mL	0.050
Snack Foods	Salty Snacks	100 mg/200 g	0.050
Soft Candy	Chocolates	100 mg/200 g	0.050

The consumption of the soy lecithin phosphatidylserine complex from all proposed food-uses was estimated using the USDA 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996) and the 1998 Supplemental Children's Survey (USDA CSFII 1998) (USDA, 2000). Combined, these surveys provide the most appropriate data for evaluating food-use and food consumption patterns in the United States, since they contain 4 years of data on individuals selected *via* stratified, multistage area probability sampling of American households within all 50 states. USDA CSFII (1994-1996, 1998) survey data were collected from individuals and households *via* 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2) throughout all 4 seasons of the year. Data were collected in person, a minimum of 3 days apart, on different days of the week, to achieve the desired degree of statistical independence. USDA CSFII (1994-1996) contains 2-day dietary food consumption data for more than 15,000 individuals of all ages, and 1-day data for 16,103 individuals. USDA CSFII (1998) contributes consumption data from an additional 5,559 children, from birth through 9 years of age, to data reported for 4,253 children of the same ages within USDA CSFII (1994-1996). The overall USDA CSFII (1994-1996, 1998) response rate for individuals selected for participation in surveys was 81.5 and 77.5% for Day 1 and Day 2, respectively.

In addition to collecting information on the types and quantities of foods being consumed, USDA CSFII (1994-1996, 1998) collected physiological and demographic information from individual participants in the survey, including sex, age, self-reported height and weight, and other variables useful in characterizing consumption. The inclusion of this information allows for further assessment of food intake based on consumption by specific population groups of interest within the total population. USDA sample weights were developed and incorporated with USDA CSFII (1994-1996, 1998) data to correct for the potential under-representation of intakes from specific population groups as a result of sample variability due to survey design, non-response, or other factors.

Approximately 96.5% of the total U.S. population was identified as potential consumers of the soy lecithin phosphatidylserine complex from all proposed food-uses (19,880 actual users identified). The consumption of all soy lecithin phosphatidylserine complex-containing foods by the total U.S. population yielded mean estimates of daily intake (all-user basis) of 0.71 g/person/day. Based on total population body weight approximations, this would correspond to an exposure of 12.8 mg/kg body weight/day. Assessment of heavy consumers (90th percentile, all-user basis) of the soy lecithin phosphatidylserine complex indicated exposures of 1.19 g/person/day, or 23.5 mg/kg body weight/day on a body weight basis (see Tables 4 and 5). Based on the composition of the soy lecithin phosphatidylserine complex (approximately 20% phosphatidylserine), these estimates would provide phosphatidylserine mean and 90th percentile intakes of approximately 140 mg/person/day (2.6 mg/kg body weight/day) and 240 mg/person/day (4.7 mg/kg body weight/day), respectively.

Table 4 Summary of the Estimated Daily Intake of Soy Lecithin Phosphatidylserine Complex from All Proposed Food Categories in the United States by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (g)	90th Percentile (g)	Mean (g)	90th Percentile (g)
Infant	0-2	79.8	2,857	0.33	0.65	0.39	0.68
Children	3-11	100	6,304	0.52	0.78	0.52	0.78
Female Teenager	12-19	100	702	0.59	0.93	0.59	0.93
Male Teenager	12-19	100	696	0.87	1.44	0.87	1.44
Female Adult	20 and Up	100	4,572	0.66	1.04	0.66	1.04
Male Adult	20 and Up	100	4,749	0.86	1.41	0.86	1.41
Total Population	All Ages	96.5	19,880	0.70	1.19	0.71	1.19

Table 5 **Summary of the Estimated Daily Per Kilogram Body Weight Intake of Soy Lecithin Phosphatidylserine Complex from All Proposed Food Categories in the United States by Population Group (1994-1996, 1998 USDA CSFII Data)**

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Infant	0-2	79.8	2,857	26.6	53.1	31.4	55.3
Children	3-11	100	6,304	21.3	34.9	21.3	34.9
Female Teenager	12-19	100	702	10.7	18.0	10.7	18.0
Male Teenager	12-19	100	696	13.7	23.6	13.7	23.6
Female Adult	20 and Up	100	4,572	10.1	16.6	10.1	16.6
Male Adult	20 and Up	100	4,749	10.5	17.6	10.5	17.6
Total Population	All Ages	96.5	19,880	12.7	23.4	12.8	23.5

This type of intake methodology is generally considered to be 'worst case' as a result of several conservative assumptions made in the consumption estimates. For example, it is often assumed that all food products within a food category contain the ingredient at the maximum specified levels of use. In addition, it is well established that the length of a dietary survey affects the estimated consumption of individual users. Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate consumption of food products that are consumed relatively infrequently.

Since the soy lecithin phosphatidylserine complex is essentially enzymatically-modified soy lecithin with added serine, the estimated intake of the complex also was compared to intake levels of soy lecithin from natural sources, as well as from its addition to foods. The safety of lecithin was last evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1973 (JECFA, 1974), at which point daily lecithin intakes from a typical diet in the range of 1 to 5 g were reported. In another study also based on data from the 1970's, it was estimated that approximately 6 g of soy lecithin was provided daily in the American diet (Zeisel *et al.*, 1982). Although it has been noted that eating patterns have changed over the last few decades and, thus, present soy lecithin intake levels may not be adequately represented by such older data, it is expected that reductions in soy lecithin intake as for example by decreasing consumption of cholesterol-containing foods, which also are considered to be rich sources of dietary lecithin, will have been offset by increased intake of lecithin-containing food supplements and processed foods (Wurtman, 1979). The estimated consumption of the soy lecithin phosphatidylserine complex at the 90th percentile level (1.19 g/person/day), therefore, approximates the intake of soy lecithin from combined dietary sources.

[redacted]

In 1998, the Institute of Medicine (IOM) established adequate daily intake levels for choline of 550 and 425 mg for men and women, respectively, and an upper intake level (UL) of 3.5 g/day. The phosphatidylcholine content of the raw material is reported to be approximately 40% (IOM, 1998). In order to compare potential choline residual levels in the complex to the UL, it was assumed that phosphatidylserine is obtained solely as a result of the replacement of the ethanolamine moiety of phosphatidylethanolamine with all of the initial phosphatidylcholine content remaining unchanged in the final product. Based on this maximum level assumption, the mean and 90th percentile total population all-user intake of phosphatidylcholine from the consumption of the soy lecithin phosphatidylserine complex would correspond to 284 and 476 mg/person/day (5.12 and 9.4 mg/kg body weight/day), respectively. Since phosphatidylcholine contains approximately 13% of choline by weight (Canty *et al.*, 1994), the corresponding 90th percentile intake of choline from the soy lecithin phosphatidylserine complex is approximately 62 mg/day. As this maximum theoretical intake is 56-fold lower than the UL, choline residues that may remain in the product following washing is not a concern. Realistically, phosphatidylserine would be formed from both phosphatidylcholine and phosphatidylethanolamine and the dissociated choline would be expected to be washed out thereby resulting in considerably lower choline exposures.

DATA PERTAINING TO SAFETY

The assessment of the safety of the soy lecithin phosphatidylserine complex was based on a series of short- and long-term animal toxicity studies and *in vitro* and *in vivo* short-term assays for mutagenicity/genotoxicity conducted by Heywood *et al.* (1987), as well as several human clinical trails. The human studies were designed predominantly to evaluate the potentially beneficial properties of phosphatidylserine on cognitive function in elderly subjects; however, in most instances, subjects also were monitored for the occurrence of any adverse effects, and blood chemistry and urinalysis were usually performed. The majority of clinical studies, as well as the series of animal toxicity studies, was conducted with phosphatidylserine derived *via* extraction from bovine brain tissue. A number of clinical studies, including several published and unpublished trials performed specifically with Lipogen's soy lecithin phosphatidylserine, have evaluated the safety or efficacy of phosphatidylserine obtained from soy lecithin.

Differences in the fatty acid composition have been identified between phosphatidylserine obtained from brain tissue *versus* plant sources. These differences could potentially impact the efficacy of phosphatidylserine complexes. However, such differences in the fatty acid composition are not expected to affect the safety of phosphatidylserine. This conclusion is based on the fact that the fatty acids of the phosphatidylserine component of both the bovine- and soy-derived products will be cleaved from the phospholipids prior to absorption. The free fatty acids are subsequently similarly processed by the body irrespective of their source. Furthermore, with the exception of the exogenously added serine, all the individual components of the soy lecithin phosphatidylserine complex, including the fatty acids, occur naturally in soy

lecithin, which is GRAS. Docosahexaenoic acid (DHA) is considered to be characteristic of brain tissue-derived phosphatidylserine; soy lecithin phosphatidylserine predominantly contains linoleic acid and α-linolenic acid, which are essential polyunsaturated fatty acids that must be provided in the diet. Also, α-linolenic acid is a metabolic precursor to DHA. Therefore, given the overall structural similarity between soy and bovine phosphatidylserine, as well as a similar metabolic fate, principally resulting in the degradation of the phospholipids to common metabolites, all studies support the safety of soy lecithin phosphatidylserine. It should also be noted that the fatty acids, linoleic acid and α-linolenic acid, contributed to the diet from proposed uses of Lipogen's soy phosphatidylserine complex are well below the adequate intakes (AI) established by the IOM (2002) for these fatty acids.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION (ADME)

Following intravenous administration to rats and mice, phosphatidylserine was demonstrated to be eliminated from plasma in a biphasic manner and to be largely distributed to several major organs including the liver, spleen, and brain tissue (Orlando *et al.*, 1975; Mazzari *et al.*, 1982; Toffano *et al.*, 1982, 1987; Palatini *et al.*, 1991). *In vitro* assays have demonstrated efficient incorporation of exogenous phosphatidylserine into cell membranes (Vecchini *et al.*, 1982). Following incubation, double-isotope labeled phosphatidylserine was shown to be incorporated in the membranes of cultured neuroblastoma cells, with only a small portion subject to decarboxylation (Vecchini *et al.*, 1982). In contrast, orally administered phosphatidylserine, as all other dietary phospholipids, is extensively hydrolyzed by phospholipase A_2 to *lyso*phosphatidylserine in the gastrointestinal tract prior to absorption (Orlando *et al.*, 1975; Bruni *et al.*, 1990, 1992; IOM, 2002).

In mammalian cells, phosphatidylserine may undergo decarboxylation to phosphatidylethanolamine in the mitochondria, which is subsequently followed by potential re-formation of phosphatidylserine through exchange of the ethanolamine moiety with serine in the endoplasmic reticulum or mitochondria-associated membrane (Kuge and Nishijima, 2003). Thus, in the intestinal absorptive cells, *lyso*phosphatidylserine may be reacylated to yield phosphatidylserine and ultimately converted to phosphatidylethanolamine (Bruni *et al.*, 1990, 1992). Re-esterified phospholipids are subsequently incorporated into intestinal lipoproteins (*i.e.*, chylomicrons) or directly transported as *lyso*phospholipids *via* the portal system to the liver (Linder, 1991; Krummel, 1996; IOM, 2002). Chylomicrons are released into the circulation *via* the thoracic duct (Linder, 1991). As the chylomicrons circulate in the blood, its components including phospholipids are degraded *via* lipoprotein lipase (LPL) hydrolytic activity (Krummel, 1996). Ultimately the phosphatidylserine degradation products (*i.e.*, free fatty acids, serine, glycerol, and phosphorus-containing substances) enter common physiological pathways of amino acid and lipid metabolism. Intact phospholipids, in turn, are excreted in the bile and thus, may be subject to enterohepatic circulation.

Studies in animals receiving intravenous administrations of phosphatidylserine indicate that phospholipids also undergo hydrolytic cleavage to the monoacyl derivative *lyso*phosphatidylserine in the plasma, as well as decarboxylation of the serine moiety to phosphatidylethanolamine in circulating blood cells (Mazzari *et al.*, 1982; Toffano *et al.*, 1982; Palatini *et al.*, 1991). *lyso*Phosphatidylserine and phosphatidylethanolamine also were detected in the liver and brain tissues following intravenous administration. In all organs, however, the majority of radioactivity (approximately 90%) was consistently accounted for by unmetabolized phosphatidylserine (Toffano *et al.*, 1987; Palatini *et al.*, 1991). In contrast, although at 60 minutes following oral administration of phosphatidylserine to rats at a dose level of 20 mg/kg body weight, the majority of the circulating plasma radioactivity also consisted of phosphatidylserine, the radioactivity at 24 hours was predominantly due to phosphatidylserine degradation products (Toffano *et al.*, 1987). Moreover, less than 20% of the administered dose recovered in the mesenteric lymph of rats following oral administration of phosphatidylserine (50 mg/kg body weight of [^{3}H]-glycerol-labeled brain-derived phosphatidylserine) was liposoluble, with phospholipids specifically comprising only 11% of the liposoluble fraction (Bruni *et al.*, 1992). The majority of the radioactivity was recovered as triglycerides, and to a smaller extent diacylglycerol, indicating complete degradation of orally administered phosphatidylserine. In humans, oral consumption of 5 soy lecithin phosphatidylserine capsules, providing a total of 500 mg phosphatidylserine, resulted in peak plasma phosphatidylserine levels of 3.95% of the total phospholipid plasma concentration in comparison to background phosphatidylserine levels of 1.8 to 2.2% of total plasma phospholipids (Shinitzky, 1999).

The effect of bovine derived phosphatidylserine on the release of acetylcholine from the cerebral cortex of the rat was evaluated in animals injected intravenously with sonicated suspensions of phosphatidylserine at doses of 75 and 150 mg/kg bodyweight (Casamenti *et al.*, 1979). The results of this study demonstrated that phosphatidylserine caused a dose dependent, calcium dependent increase in acetylcholine output. As *in vitro* studies indicated no effect of phosphatidylserine on acetylcholine release from brain slices, the response observed *in vivo* is not likely to occur due to a direct response. Thus, the authors concluded that phosphatidylserine exerts an indirect stimulating action on a septo-cortical cholinergic pathway. In comparison, phosphatidylethanolamine was about half as active as phosphatidylserine and phosphatidylcholine had no effect.

Following metabolism, hydrosoluble metabolites are excreted in the urine, whereas the liposoluble fraction is eliminated *via* the feces. In rats, approximately 60% of an orally administered dose of phosphatidylserine (20 mg/kg body weight) was recovered in the feces, of which 50% was identified as *lyso*phosphatidylserine, and only 10% was detected in the urine (Toffano *et al.*, 1987).

TOXICOLOGICAL STUDIES

Acute Studies

In rodents, oral administration of phosphatidylserine complex was associated with a very low order of acute toxicity (*i.e.*, greater than 2 g/kg body weight). Specifically, results of acute toxicity studies demonstrated oral LD_{50} values of greater than 5 and 2 g/kg body weight in rats and rabbits, respectively (Heywood *et al.*, 1987). Administered intravenously, a LD_{50} of 236 mg/kg body weight was reported for rats (Heywood *et al.*, 1987).

Following subcutaneous injection of phosphatidylserine liposomes, at the dose level of 25 mg/kg body weight, inhibition of the adaptive immune response following immunization (*i.e.*, reductions in the draining lymph node tissue mass, accompanied by reduced numbers of total leukocytes and antigen-specific $CD4^+$ T cells, as well as decreased formation and size of spleen and lymph node germinal centers, and blood levels of antigen-specific IgG), was reported in mice (Hoffmann *et al.*, 2005). There is no expectation of similar effects following oral dosing given that phosphatidylserine is degraded prior to absorption.

Subchronic and Chronic Studies

Heywood *et al.* (1987) completed a series of subchronic and chronic experiments in rats and dogs in order to assess the potential toxicity of a bovine cortex-derived phosphatidylserine complex following oral, as well as parenteral administration. In a 26-week study, Sprague-Dawley rats were administered the phosphatidylserine complex at dose levels of 0 (control), 10, 100, or 1,000 mg/kg body weight/day *via* gavage. Excessive salivation was observed following administration of the phosphatidylserine complex. In comparison to control animals, blood chemistry results and urinalysis revealed enhanced alkaline phosphatase (ALP) activity and a reduction in the urinary pH, respectively, in both sexes of high-dose animals (*i.e.*, 1,000 mg/kg body weight/day). Increased serum potassium levels, and decreased levels of serum albumin and sodium were limited to male rats of the high-dose group. Ophthalmoscopic examination, as well as macroscopic and microscopic evaluations were unremarkable. In a 1-year-long oral toxicity study, groups of beagle dogs received daily gavage administrations of 0 (control), 10, 100, or 1,000 mg/kg body weight of the phosphatidylserine complex. Following treatment administration, vomiting and loose feces were reported in test animals. Suppression of appetite observed during the first week of treatment was accompanied by a significant decrease in body weights in males and females receiving the phosphatidylserine complex at a dose level of 1,000 mg/kg body weight/day. Findings were limited to significant reductions in blood glucose and cholesterol levels in high-dose males and females. No other variations were observed, including no gross or microscopic abnormalities and no organ weight variations in any test group.

In addition to the oral toxicity studies, several studies were conducted in which animals received intravenous or intramuscular injections of the bovine brain phosphatidylserine complex (Heywood *et al.*, 1987). No toxicologically significant adverse effects were reported in either Sprague-Dawley rats or beagle dogs receiving intravenous injections of the phosphatidylserine complex at dose levels of 5 mg/kg body weight/day for a period of 4 weeks. At higher dose levels (*i.e.*, 20 and 80 mg/kg body weight/day) redness and swelling of paws and around muscle were observed in rats. In both sexes at the high-dose level and in males at the mid-dose level, variations were reported in several hematological and blood chemistry parameters. Several organ weight variations, including elevated spleen weights, also were observed in both sexes of rats at the mid- and high-dose levels (*i.e.*, 20 and 80 mg/kg body weight/day, respectively). Furthermore, in high-dose animals, increased incidences of extra-medullary hemopiesis (*i.e.*, development of blood cells) of the spleen were reported. Dogs were reported to exhibit generalized muscle tremors following treatment administration at the mid- and high-dose levels (*i.e.*, 15 and 40 mg/kg body weight/day, respectively), and significant reductions in body weights, and food and water consumption. Additionally, dose-dependent increases in the incidence of polymorphonuclear leukocyte-aggregations in the sinusoidal cavity of the liver were observed in mid- and high-dose dogs (*i.e.*, 1/12 and 4/12 dogs, respectively). Elevated white blood cell counts and reduced levels of serum protein were limited to animals treated at the high-dose level.

Likewise, in dogs receiving intramuscular injections of the phosphatidylserine complex at dose levels of 0 (control), 5, 10, or 15 mg/kg body weight/day for a period of 13 weeks, increases in leukocyte levels and erythrocyte sedimentation rates were observed in high-dose dogs (*i.e.*, 15 mg/kg body weight/day) (Heywood *et al.*, 1987). Furthermore, gross examination revealed dose-dependent increases in the incidence of subcutaneous hemorrhage and adhesion between the skin and muscles at the injection site, whereas morphological abnormalities, which also were confined to the site of injection, consisted of muscle degeneration, subcutaneous and intramuscular acute inflammatory cell infiltration and necrosis. Given the route of administration used in this study, these findings are not relevant for orally administered phosphatidylserine.

Reproductive and Developmental Studies

The potential reproductive toxicity and teratology of brain-derived phosphatidylserine were investigated in rats and rabbits following maternal gavage of the phospholipid complex at dose levels of 0, 10, 100, or 200, and 0, 50, 150, or 450 mg/kg body weight/day, respectively (Heywood *et al.*, 1987). Treatment was initiated on day 6 of gestation and continued through days 15 and 18 for rats and rabbits, respectively. Rats and rabbits were subsequently necropsied and fetuses removed on days 20 and 29, respectively. No statistically significant variations were observed in either species of laboratory animal. Rabbit fetal body weights were reduced at the 450 mg/kg body weight/day dose level, albeit not at levels of statistical significance. Fetal body weight variations occurred in the presence of body weight gain

reductions observed in high-dose dams during the first 4 days of treatment. In another study evaluating the development of mice, no differences in the onset of reflexes, and no variations in body weights were observed in nursing pups 30 days following birth whose mothers received 50 mg/kg body weight/day of bovine brain phosphatidylserine complex in aqueous solution beginning on the day of parturition (Fagioli *et al.*, 1989; Ammassari-Teule *et al.*, 1990). These data support that phosphatidylserine is not a reproductive or developmental toxicant.

Genotoxicity Studies

Results of *in vitro* assays for mutagenic and clastogenic activity were consistently negative following incubation of mammalian cells (human and mouse cells) with the brain-derived phosphatidylserine complex in the absence and presence of metabolic activation (Heywood *et al.*, 1987). Likewise, in mice, the phosphatidylserine complex did not induce an increase in micronucleus frequency in bone marrow cells following 2 successive gavage administrations of the complex at dose levels of 15, 75, or 150 mg/kg body weight in comparison to controls.

Summary of Toxicological Assessment

The above studies, which were conducted by a reputable contract research organization and include the study of standard toxicological endpoints in several species, several routes of administration using multiple doses, and different durations of treatment, up to one year, support the safety of phosphatidylserine for addition to foods. Based on the absence of any toxicologically significant adverse effects, results of the 26-week rat and the 1-year dog gavage studies support a no-observed-adverse-effect level (NOAEL) of 1,000 mg/kg body weight/day for a phosphatidylserine preparation from bovine brain (Heywood *et al.*, 1987).

Clinical Studies

As a result of a potentially beneficial effect of phosphatidylserine on cognitive function, a number of open-label and placebo-controlled double-blind studies have been conducted in humans to assess the efficacy of orally administered phosphatidylserine. The majority of trials available were performed with brain-extracted phosphatidylserine complexes (Delwaide *et al.*, 1986; Allegro *et al.*, 1987; Fünfgeld and Nedwidek, 1987; Palmieri *et al.*, 1987; Puca *et al.*, 1987; Ransmayr *et al.*, 1987; Sinforiani *et al.*, 1987; Crook *et al.*, 1991, 1992; Cenacchi *et al.*, 1993). There were also several studies, including studies performed with Lipogen's soy lecithin phosphatidylserine complex, in which subjects received plant source-derived phosphatidylserine (Gindin *et al.*, 1992, 1994, 2000; Shinitzky, 1999; Schreiber *et al.*, 2000; Benton *et al.*, 2001; Jorissen *et al.*, 2002; Hellhammer *et al.*, 2004).

In a 12-week study performed by Jorissen *et al.* (2002), in which test groups were provided daily 300 or 600 mg of soy lecithin-derived phosphatidylserine, no clinically significant variations were reported in blood chemistry or hematology, and no differences were noted in the occurrence of side effects among the test and placebo groups. In the remaining studies conducted with

phosphatidylserine of plant origin, evaluation of safety following daily treatment with phosphatidylserine over periods of 21 days to more than a year was limited to a subjective assessment of tolerability. Gastrointestinal disturbances consisting mainly of flatulence were reported in a 12-week study conducted with individuals exhibiting cognitive decline, in which test subjects consumed 300 mg of phosphatidylserine/day; however, the study protocol did not include a group of placebo patients (Schreiber *et al.*, 2000). Thus, the absence of a placebo group precluded a conclusion as to whether or not gastrointestinal side effects reported in subjects receiving phosphatidylserine were treatment-related. In another study recruiting healthy young adult males, side effects were reported to occur in placebo, but not in soy lecithin phosphatidylserine-treated (300 mg/day) subjects (Benton *et al.*, 2001). Additionally, no side effects related to the oral administration of Lipogen's soy lecithin phosphatidylserine complex at dose levels providing up to 800 mg phosphatidylserine/day for periods of 3 weeks to more than 1 year were reported (Gindin *et al.*, 1994, 2000; Hellhammer *et al.*, 2004). Likewise, in an efficacy study also conducted with Lipogen's soy lecithin phosphatidylserine complex, there was no indication of the occurrence of any adverse side effects in test subjects receiving daily 300 mg of phosphatidylserine (Gindin *et al.*, 1992, 1993). Moreover, test subjects experienced significant improvements in memory and mood. No adverse effects were reported by study participants in a single-dose study conducted to assess the absorption of phosphatidylserine provided as part of Lipogen's soy lecithin phosphatidylserine complex (Shinitzky, 1999).

A number of studies performed with phosphatidylserine extracted from animal brain tissues, support the safety of orally administered phosphatidylserine. In a series of double-blind studies up to 6 months in duration in which study subjects were provided daily doses of 300 mg of phosphatidylserine from brain extracts, the phosphatidylserine complexes were generally reported to be well tolerated and no significant side effects were observed (Delwaide *et al.*, 1986; Palmieri *et al.*, 1987; Ransmayr *et al.*, 1987; Crook *et al.*, 1991, 1992; Cenacchi *et al.*, 1993). A single incident of dizziness in a group of 215 phosphatidylserine-treated test subjects was reported in the study conducted by Cenacchi *et al.* (1993). Gastrointestinal side effects in the Cenacchi *et al.* (1993) study were limited to subjects in the placebo study group, whereas in the study performed by Ransmayr *et al.* (1987) incidences of gastrointestinal discomfort were reported in both the test and placebo subjects. In 2 studies in which blood chemistry parameters also were monitored, no variations related to treatment with phosphatidylserine were noted (Palmieri *et al.*, 1987; Cenacchi *et al.*, 1993).

The safety and tolerability of phosphatidylserine is further corroborated by a number of open-label trials, in which individuals also were provided brain-derived phosphatidylserine for oral consumption at daily dose levels of up to 500 mg with treatment extending over periods of up to 60 days (Allegro *et al.*, 1987; Fünfgeld and Nedwidek, 1987; Puca *et al.*, 1987; Sinforiani *et al.*, 1987). No side effects were reported and in cases where blood chemistry was evaluated, results in comparison to baseline values were unremarkable. In an additional study, 50 mg/day of phosphatidylserine (source not specified) was intramuscularly administered to women for a

period of 30 days (Manfredi *et al.*, 1987). As in the trials in which phosphatidylserine was provided in capsules for oral administration, blood chemistry and hematology analyses were unremarkable, and phosphatidylserine treatment was well tolerated.

Additionally, a number of efficacy studies were conducted with phosphatidylserine complexes orally administered at dose levels of up to 500 mg for periods of up to 60 days to elderly patients exhibiting cognitive decline in which no adverse effects were apparent (Caffarra and Santamaria, 1987; Granata and Di Michele, 1987; Villardita *et al.*, 1987; Engel *et al.*, 1992; Heiss *et al.*, 1993, 1994); however, in these studies the authors did not indicate whether the occurrence of adverse effects was monitored. In the 6-month study conducted by Heiss *et al.* (1994), in which phosphatidylserine was provided to subjects at dose levels of 400 mg/day, complete blood cell counts and routine blood chemistry were performed once every 4 weeks during the treatment period; however, results of the clinical chemistry evaluations were not discussed.

In addition to the data reported in the individual studies, Cennachi *et al.* (1987) assessed the human tolerability of bovine brain cortex-derived phosphatidylserine provided at daily dose levels of 300 mg for a period of 6 weeks by collectively analyzing results obtained for several common clinical chemistry parameters [*i.e.*, blood cell count, glucose, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, creatinine, bilirubin, cholesterol, and triglycerides], as evaluated by a number of different investigators encompassing a total of 130 patients (65M, 65F). Although treatment with phosphatidylserine was reported to induce significant reductions in both uric acid levels and serum ALT activity in adult males in comparison to baseline values, the biochemical variations were determined to have no clinical relevance.

Although the Physicians' Desk Reference for Nutritional Supplements (PDRNS) reports rare cases of gastrointestinal disturbances, particularly nausea, occurring as a result of phosphatidylserine stimulation of dopamine release following ingestion of larger doses (*i.e.*, 200 mg per single dose or higher), the occurrence of side effects related to gastrointestinal function as a result of phosphatidylserine ingestion was not confirmed in any of the human clinical trials. Since the purpose of most of the trials was to assess the efficacy of phosphatidylserine with respect to improvement of neurological function and of age-related memory decline, subjects typically were elderly patients with a range of neurological disorders (*i.e.*, Parkinson's, Alzheimer's disease) or other underlying medical conditions. In spite of the participation of study populations with somewhat compromised health, no significant adverse effects were reported in any of the studies. Moreover, in several of the clinical trials, subjects were permitted to continue taking their usual medications for the various pre-existing medical conditions. With the exception of blood pressure fluctuations observed in some hypertensive subjects in the study performed by Ransmayr *et al.* (1987), requiring adjustment of the dosages of antihypertensive agents, no interactions with any other medications were observed.

Moreover, in the study in which blood pressure variations were reported, it was not specified whether variations occurred in the placebo or test groups. Furthermore, it is possible that the fluctuations occurred as a result of alterations in the patients' health, rather than as a result of an interaction between phosphatidylserine and the antihypertensive agents.

On the basis of the existing data from animal studies and the knowledge that phosphatidylserine is a component of the diet including breast milk, there is no reason to expect any potential unusual susceptibilities among diverse populations.

SUMMARY

Lipogen intends to market a complex of phosphatidylserine, an endogenously occurring amino phospholipid, as an ingredient in food in order to increase the dietary intake of phosphatidylserine in the general population. The phosphatidylserine complex is intended to be added to a variety of food products including baked goods, beverages, cereals, cheese, coffee, tea, condiments, fats, oils, jams, milk, dairy product analogs, processed fruits and fruit juices, snack foods, soft candy, and grain, nut, plant protein and milk products. Depending on the particular food category, the soy lecithin phosphatidylserine complex is proposed for use as a food ingredient at use levels of up to 0.50% per serving. Although soy lecithin-derived phosphatidylserine is not currently an ingredient added to food in the United States, unmodified soy lecithin and enzymatically-transformed soy lecithin using phospholipase A_2 and pancreatin are affirmed as GRAS. Under the conditions of intended use of Lipogen's soy lecithin phosphatidylserine complex, the total population all-user mean intake is estimated to be 0.71 g/person/day or 12.8 mg/kg body weight/day. The heavy consumer (90^{th} percentile) all-user intake of the soy lecithin phosphatidylserine complex from all proposed food-uses is estimated to be 1.19 g/person/day or 23.5 mg/kg body weight/day. Based on the composition of the soy lecithin phosphatidylserine complex (approximately 20% phosphatidylserine), these estimates would provide phosphatidylserine mean and 90^{th} percentile intakes of 140 mg/person/day (2.6 mg/kg body weight/day) and 240 mg/person/day (4.7 mg/kg body weight/day), respectively. Phosphatidylserine is a phospholipid identified to occur naturally in human, as well as other animal and plant cells, where it functions as an essential structural component of cell membranes. Given its natural occurrence in commonly consumed foods such as meats, egg, and soy, phosphatidylserine is consumed as part of the habitual diet.

The soy lecithin phosphatidylserine complex is produced by Lipogen in accordance with current good manufacturing practices (GMPs) and meets appropriate food-grade specifications. The manufacturing process consists of an enzymatic modification of soy lecithin *via* phospholipase D activity derived from cabbage extract. Specifically, the enzyme catalyzes the hydrolysis of phosphatidylcholine or phosphatidylethanolamine resulting in the release of the choline and ethanolamine moieties, respectively, and formation of phosphatidic acid, which is subsequently esterified with exogenously added serine. Once complete, the enzymatic activity is terminated, and the resulting soy lecithin phosphatidylserine complex is subject to purification and drying,

and is ultimately formulated into a liquid or powder product. In order to ensure a consistent product, Lipogen has established numerous chemical and microbiological specification parameters for the final formulated liquid and powder soy lecithin phosphatidylserine complexes. Batch samples are routinely assayed to verify that the set limits are met, ensuring a safe product.

From data available on the absorption, metabolism, and elimination of orally administered phosphatidylserine, results indicate that only a relatively minor portion of phosphatidylserine is absorbed systemically unmetabolized. The majority of an oral dose of the phospholipid is subject to extensive hydrolysis in the gastrointestinal tract, resulting among other degradation products in the formation of *lyso*phosphatidylserine. Moreover, phosphatidylserine also may undergo decarboxylation to phosphatidylethanolamine in the absorptive epithelial cells of the intestine. Following systemic absorption, phosphatidylserine and its metabolites enter the circulation *via* the lymphatic system or hepatic portal vein. Following oral treatment only 18% of the administered dose recovered in lymph was liposoluble with 80% consisting of triglycerides, indicating complete degradation of phosphatidylserine and use of the glycerol fraction in *de novo* synthesis. Thus, the majority of orally administered phosphatidylserine was converted to hydrophilic metabolites.

Results of animal toxicity studies indicated some adverse effects following intravenous and intramuscular injection of phosphatidylserine (Heywood *et al.*, 1987). However, these results are not relevant to the oral route of exposure, particularly in light of the limited absorption of unhydrolyzed phosphatidylserine. Likewise, although following subcutaneous injection of phosphatidylserine liposomes at dose levels of 25 mg/kg body weight, inhibition of immune responses was reported in mice (Hoffmann *et al.*, 2005), given the extensive degradation and highly limited systemic absorption of phosphatidylserine following oral administration, it is not expected that phosphatidylserine from its use a food additive would significantly alter immune system function. In contrast, following oral administration of phosphatidylserine to rats and dogs at dose levels of up to 1,000 mg/kg body weight/day for a period of up to 1 year, statistically significant variations were limited to fluctuations in isolated clinical chemistry and urinalysis parameters at the highest dose level and in no case were accompanied by any organ weight differences, or macroscopic or histopathological abnormalities (Heywood *et al.*, 1987).

Additionally, results of *in vitro* and *in vivo* mutagenicity and genotoxicity assays conducted with bovine cortex-derived phosphatidylserine were unequivocally negative (Heywood *et al.*, 1987). No variations in several reproductive parameters and no teratological abnormalities were observed in rodents following administration of phosphatidylserine during gestation (Heywood *et al.*, 1987). Administration of phosphatidylserine to lactating mice also did not adversely affect pup development (Fagioli *et al.*, 1989; Ammassari-Teule *et al.*, 1990).

Moreover, for purposes of assessing the potentially beneficial effect of phosphatidylserine with respect to neurological function, phosphatidylserine complexes have been extensively studied in

human trials. Although most clinical studies were conducted with phosphatidylserine extracted from brain tissue, a number of studies was conducted with plant source-derived phosphatidylserine, including published and unpublished studies in which subjects received Lipogen's soy lecithin phosphatidylserine, with one study focusing specifically on the safety of soy lecithin phosphatidylserine (Jorissen *et al.*, 2002). During the 12-week treatment period, study participants received 3 times daily 2 gelatin capsules containing food-grade phosphatidylserine powder (40% of pure phosphatidylserine) in amounts providing 50 or 100 mg of phosphatidylserine. Thus, in total, study participants received daily doses of 300 or 600 mg of phosphatidylserine. Following the treatment period, hematology and blood biochemistry did not reveal any statistically significant variations in comparison to the placebo group, and all fluctuations were reported to remain within the normal limits of variation. Specifically, the blood chemistry variations observed in orally treated animals were not confirmed by studies conducted in human subjects. Furthermore, phosphatidylserine administration did not adversely affect vital signs and the total number of side effects reported by test subjects did not differ significantly from study participants receiving placebo capsules. In the studies conducted with Lipogen's soy lecithin phosphatidylserine, no side effects related to the oral administration of phosphatidylserine at dose levels of up to 800 mg/day were reported (Gindin *et al.*, 1994, 2000; Hellhammer *et al.*, 2004). Given the overall structural similarities between soy lecithin- and brain cortex-derived phosphatidylserine, the safety of phosphatidylserine is additionally supported by the results of double-blind and open-label efficacy trials in which brain tissue-derived phosphatidylserine complexes at dose levels of up to 500 mg/day were not associated with any treatment-related adverse effects.

Based on the absence of any toxicologically significant adverse effects, results of the 26-week rat and the 1-year dog gavage studies support a no-observed-adverse-effect level (NOAEL) of 1,000 mg/kg body weight/day for a phosphatidylserine preparation from bovine brain (Heywood *et al.*, 1987). Estimates of intake under the intended conditions of use of the soy lecithin phosphatidylserine complex indicate an all-user intake level of 23.5 mg/kg body weight/day for the heavy-end consumer (90th percentile). Accordingly, the NOAEL of 1,000 mg/kg body weight/day is several fold greater than the 90th percentile estimated intake level of the soy lecithin phosphatidylserine complex from its addition to food. Moreover, the daily dose levels of pure phosphatidylserine (*i.e.*, up to 600 mg/day) obtained from a soy lecithin powder which did not induce any clinically significant adverse effects in humans following a 12-week treatment period (Jorissen *et al.*, 2002), exceed the estimated all-user intake of Lipogen's soy lecithin phosphatidylserine complex (*i.e.*, 240 mg/person/day at the 90th percentile) by 2.5-fold.

Overall, when viewed in its entirety, the scientific evidence presented above indicates that under the conditions of intended use in foods, the soy lecithin phosphatidylserine complex would reasonably be expected to be safe. The bioavailability of orally ingested unmetabolized phosphatidylserine is largely limited by extensive hydrolysis in the gastrointestinal tract prior to absorption. The safety of the soy lecithin phosphatidylserine complex is confirmed by a series

of published short- and long-term animal toxicity studies, as well as human clinical trials, consistently reporting no toxicologically significant adverse effects relevant to the conditions of intended use in foods. The total body of published data and information summarized in this report demonstrates that the soy lecithin phosphatidylserine complex meeting appropriate food-grade specifications is GRAS, based on scientific procedures, under the conditions of intended use in foods.

CONCLUSION

We, the Expert Panel, have independently and collectively, critically evaluated the data and information summarized above and conclude that Lipogen's soy lecithin phosphatidylserine complex, meeting appropriate food grade specifications and produced in according with current good manufacturing practice, is Generally Recognized as Safe (GRAS) based on scientific procedures under the conditions of intended use in foods specified herein.

11/18/2005

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REFERENCES

Allegro, L.; Favaretto, V.; Ziiliotto, G. 1987. Oral phosphatidylserine in elderly patients with cognitive deterioration: An open study. Clin Trials J 24(1):104-108.

Ammassari-Teule, M.; Fagioli, S.; Maritati, M.; Populin, R.; Pavone, F. 1990. Chronic administration of phosphatidylserine during ontogeny enhances subject-environment interactions and radial maze performance in C57BL/6 mice. Physiol Behav 47(4):755-760.

Benton, D.; Donohoe, R.T.; Sillance, B.; Nabb, S. 2001. The influence of phosphatidylserine supplementation on mood and heart rate when faced with an acute stressor. Nutr Neurosci 4:169-178.

Bruni, A.; Bellinin, F.; Mietto, L.; Boarato, E.; Viola, G. 1990. Phospholipid absorption and diffusion through membranes. In: Hanin, I.; Pepeu, G. (Eds.). Phospholipids. Biochemical, pharmaceutical, and Analytical Considerations. New York: Plenum Press pp. 59-68.

Bruni, A.; Orlando, P.; Mietto, L.; Viola, G. 1992. Phospholipid metabolism in rat intestinal mucosa after oral administration of lysophospholipids. In: Bazan, N.G. (Ed.) Neurobiology of Essential Fatty Acids. New York: Plenum Press, 243-249.

Caffarra, P.; Santamaria, V. 1987. The effects of phosphatidylserine in patients with mild cognitive decline: An open trial. Clin Trials J 24(1):109-114.

Canty, D.J.; Zeisel, S.H. 1994. Lecithin and choline in human health and disease. Nutr Rev 52(10):327-339.

Casamenti, F.; Mantovani, P.; Amaducci, L. and Pepeu, G. 1979. Effect of phosphatidylserine on acetylcholine output from the cerebral cortex of the rat. J Neurochemistry 32:529-533.

Cenacchi, T.; Baggio, C.; Palin, E. 1987. Human tolerability of oral phosphatidylserine assessed through laboratory examinations. Clin Trials J 24(1):125-130.

Cenacchi, T.; Bertoldin, T.; Farina, C.; Fiori, M.G.; Crepaldi, G. 1993. Cognitive decline in the elderly: A double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. Aging (Milano) 5(2):123-133.

CFR. 2003. Subchapter B—Food for human consumption. Part 101—Food Labeling. Section §101.12 Reference amounts customarily consumed per eating occasion. In: Code of Federal Regulations. Title 21—Food and Drugs. U.S. Government Printing Office; Washington, DC, 47-56.

CFR. 2005. [Various]. Sections §172.480, §182.3013, §182.8013, §184.1063, §184.1193 & §184.1400. In: U.S. Code of Federal Regulations Title 21: Food and Drugs. Food and Drug Administration (FDA). U.S. Government Printing Office (GPO); Washington DC.

000036

Crook, T.H.; Tinklenberg, J.; Yesavage, J.; Petrie, W.; Nunzi, M.G.; Massari, D.C. 1991. Effects of phosphatidylserine in age-associated memory impairment. Neurology 41(5):644-649.

Crook, T.; Petrie, W.; Wells, C.; Massari, D.C. 1992. Effects of phosphatidylserine in Alzheimer's disease. Psychopharmacol Bull 28(1):61-66.

Delwaide, PJ.; Gyselynck-Mambourg, AM.; Hurlet, A.; Ylieff, M. 1986. Double-blind randomized controlled study of phosphatidylserine in senile demented patients. Acta Neurol Scand 73(2):136-140.

Engel, R.R.; Satzger, W.; Gunther, W.; Kathmann, N.; Bove, D.; Gerke, S.; Munch, U.; Hippius, H. 1992. Double-blind cross-over study of phosphatidylserine vs. placebo in patients with early dementia of the Alzheimer type. Eur Neuropsychopharmacol 2(2):149-155.

Fagioli, S.; Castellano, C.; Oliverio, A.; Pavone, F.; Populin, R.; Toffano, G. 1989. Phosphatidylserine administration during postnatal development improves memory in adult mice. Neurosci Lett 101:229-233.

FDA. 2003. Phosphatidylserine and Cognitive Dysfuntion and Dementia (Qualified Health Claim: Final Decision Letter). U.S. Food and Drug Administration (FDA), CFSAN/Office of Nutritional Products, Labeling, and Dietary Supplements; Bethesda, Maryland, May 13, 2003. Available from http://vm.cfsan.fda.gov/~dms/ds-ltr36.html.

FDA. 2004. Letter Updating the Phosphatidylserine and Cognitve Function and Dementia Qualified Health Claim. U.S. Food and Drug Administration (FDA), CFSAN/Office of Nutritional Products, Labeling, and Dietary Supplements; Bethesda, Maryland, November 24, 2004. Available from: http://www.cfsan.fda.gov/~dms/ds-ltr39.html.

Fünfgeld, E.W.; Nedwidek, P. 1987. Neurohomologous phosphatidylserine in parkinsonian patients with associated disorders of cerebral metabolism - Results of a pilot study. Clin Trials J 24(1):42-61.

Gindin, J.; Novikov, M.; Kedar, D.; Walter-Ginzburg, A.; Naor, S.; Levi, S. 1992. Effect of Soy Lecithin Phosphatidylserine (PS) Complex on Memory Impairment and Mood in the Functioning Elderly. Unpublished Report. Lipogen, Ltd.; Israel.

Gindin, J.; Kedar, D.; Naor, S.; Novikov, A.; Walter-Ginzburg, A.; Levi, S. 1993. The effect of herbal phosphatidylserine on memory and mood in community elderly. Gerontologist 33(Spec. Iss. 1) [Abstract].

Gindin, J.; Naor, S.; Stovicheck, Y.; Dushenat, M.; Konstantin, N. 1994. Effect of Soy Lecithin Phosphatidylserine (PS) Treatment on Daily Functioning and Self-Reported General Condition in Patients with Alzheimer's disease. Unpublished Report. Lipogen, Ltd.; Israel.

Gindin, J.; Leah, E.; Ofir, O.; Dushenat, M. 2000. Long-Term Effects and Safety of Soy Lecithin Phosphatidylserine (PS) Treatment in Cognitively Impaired Out-Patient Geriatric Population. Unpublished Report. Lipogen, Ltd.; Israel.

000037

Granata, Q.; Di Michele, J.D. 1987. Phosphatidylserine in elderly patients: An open trial. Clin Trials J 24(1):99-103.

Harzer, G.; Haug, M; Dieterich, I.; Gentner, P.R.; 1983. Changing patterns of human milk lipids in the course of the lactation and during the day. Am J Clin Nutr 37:612-621.

Heiss, W.D.; Kessler, J.; Slansky, I.; Mielke, R.; Szelies, B.; Herholz, K. 1993. Activation PET as an instrument to determine therapeutic efficacy in Alzheimer's disease. Ann N Y Acad Sci 695:327-331.

Heiss, W.D.; Kessler, J.; Mielke, R.; Szelies, B.; Herholz, K. 1994. Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease. A neuropsychological, EEG, and PET investigation. Dementia 5(2):88-98.

Hellhammer, J.; Fries, E.; Buss, C.; Engert, V.; Tuch, A.; Rutenberg, D.; Hellhammer, D. 2004. Effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and physiological responses to metal stress. Stress 7(2):119-126.

Heywood, R.; Cozens, D.D.; Richold, M. 1987. Toxicology of a phosphatidylserine preparation from bovine brain (BC-PS). Clin Trials J 24(1):25-32.

Hoffmann, P.R.; Kench, J.A.; Vondracek, A.; Kruk, E.; Daleke, D.L.; Jordan, M.; Marrack, P.; Henson, P.M.; Fadok, V.A. 2005. Interaction between phosphatidylserine and the phosphatidylserine receptor inhibits immune responses *in vivo*. J Immunol 174(3):1393-1404.

IOM. 1998. Chapter 12: Choline. In: Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. National Academy Press (NAP); Washington, DC, pp. 390-414.

IOM. 2002. Chapter 8: Dietary Fats: Total fat and fatty acids. In: Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrients). National Academy Press (NAP); Washington, DC, pp. 335-432.

JECFA. 1974. Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. 17th JECFA Session, June 25-July 4, 1973, Geneva. Food and Agriculture Organization of the United Nations (FAO); Rome. FAO Nutrition Meetings Report Series, No. 53A / WHO Technical Report Series, No. 539 / WHO Food Additives Series, No. 5, pp. 234-236.

Jorissen, B.L.; Brouns, F.; Van Boxtel, M.P.; Riedel, W.J. 2002. Safety of soy-derived phosphatidylserine in elderly people. Nutr Neurosci 5(5):337-343.

Krummel, D. 1996. Lipids [and Polyunsaturated fatty acids]. In: Mahan, L.K.; Escott-Stump, S. (Eds.). Krause's Food, Nutrition, and Diet Therapy (9th Ed.). W.B. Saunders Company; Philadelphia/Toronto, pp. 49-62.

Kuge, O.; Nishijima, M. 2003. Biosynthetic regulation and intracellular transport of phosphatidylserine in mammalian cells. J Biochem 133(4):397-403.

000038

Linder, M.C. 1991. Nutrition and metabolism of fats. In: Linder, M.C. (Ed.). Nutritional Biochemistry and Metabolism: With Clinical Applications (2nd Ed.). Elsevier Science Publishing Company, Inc.; New York, pp. 51-84.

Manfredi, M.; Pranteda, G.; Saccà, A.; Morrone, G.; Vita, F.; Pranteda, G. 1987. Risultati clinici della fosfatidil-serina in 40 donne affette da turbe psico-organiche, in età climaterica e senile. Clin Ter 120:33-36. [English abstract only].

Mazzari, S.; Zanotti, A.; Orlando, P.; Raciti, R.; Toffano, G. 1982. Pharmacokinetics and pharmacodynamics of phosphatidylserine liposomes in mice. In: Antolini, R.; Gliozzi, A.; Gorio, A. (Eds.). Transport in Biomembranes: Model Systems and Reconstitution. Raven Press; New York, pp. 257-263.

Orlando, P.; Cerrito, F.; Zirilli, P. 1975. The fate of double-labelled brain phospholipids administered to mice. Farmaco [Prat] 30(9):451-458.

Palatini, P.; Viola, G.; Bigon, E.; Menegus, A.M.; Bruni, A. 1991. Pharmacokinetic characterization of phosphatidylserine liposomes in the rat. Br J Pharmacol 102:345-350.

Palmieri, G.; Palmieri, R.; Inzoli, M.R.; Lombardi, G.; Sottini, C.; Tavolato, B.; Giometto, G. 1987. Double-blind controlled trial of phosphatidylserine in patients with senile mental deterioration. Clin Trials J 24(1):73-83.

PDRNS. 2001. Phosphatidylserine. In: PDR For Nutritional Supplements (1st Ed.). Physicians' Desk Reference (PDR); Des Moines, Iowa/Medical Economics Data Production Company; Montvale, New Jersey. Available from: http://www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/pho_0202.shtml.

Puca, F.M.; Savarese, M.A.; Minervini, M.G. 1987. Exploratory trial of phosphatidylserine efficacy in mildly demented patients. Clin Trials J 24(1):94-98.

Ransmayr, G.; Plörer, S.; Gerstenbrand, F.; Bauer, G. 1987. Double-blind controlled trial of phosphatidylserine in elderly patients with arteriosclerotic encephalopathy. Clin Trials J 24(1):62-72.

Schreiber, S.; Kampf-Sherf, O.; Gorfine, M.; Kelly, D.; Oppenheim, Y.; Lerner, B. 2000. An open trial of plant-source derived phosphatidylserine for treatment of age-related cogntive decline. Isr J Psychiatry Relat Sci 37(4):302-307.

Shinitzky, M. 1999. Kinetics and Safety of Soy Lecithin Phoshatidylserine (PS) Absorption. Unpublished Report. Lipogen Ltd.; Israel.

Sinforiani, E.; Agostinis, C.; Merlo, P.; Gualteri, S.; Mauri, M.; Mancuso, A. 1987. Cognitive decline in ageing brain: Therapeutic approach with phosphatidylserine. Clin Trials J 24(1):115-124.

Souci, S.W.; Fachmann, E.; Kraut, H. (Founders); Scherz, H.; Senser, F. (Compilers). 2000. [Content of phosphatidylserine in: Beans, Beef, Eggs, Eel, Herring, Poultry, Mackrel, Milk]. In: Food Composition and Nutrition Tables = Die Zusammensetzung der Lebensmittel Nährwert-Tabellen = La Composition des Aliments, Tableaux des Valeurs

Nutritives (6th Rev. Compl. Ed. Ed.). CRC Press / Medpharm Scientific Publishers; Boca Raton / Stuttgart.

Toffano, G.; Battistella, A.; Mazzari, S.; Orlando, P.; Massari, P.; Giordano, C. 1982. Fate of phosphatidyl-L-(U-14C) serine in mice. In: Horrocks, L.A.; Ansell, G.B.; Porcellati, G. (Eds.). Phospholipids in The Nervous System: Vol. 1. Raven Press; New York, pp. 173-180.

Toffano, G.; Battistella, A.; Orlando, P. 1987. Pharmacokinetics of radiolabelled brain phosphatidylserine. Clin Trials J 24(1):18-24.

USDA. 2000. 1994-1996, 1998 Continuing Survey of Food Intakes by Individuals (CSFII) and Diet and Health Knowledge Survey (DHKS) (On CD-ROM). U.S. Department of Agriculture (USDA); Riverdale, Maryland. [PB2000-500027].

Vecchini, A.; Orlando, P.; Binaglia, L.; Massari, P.; Giordano, C.; Porcellati, G. 1982. Interaction of cultured neuroblastoma cells with sonicated phosphatidylserine. In: Horrocks, L.A.; Ansell, G.B.; Porcellati, G. (Eds.). Phospholipids in The Nervous System: Vol. 1. Raven Press; New York, p. 356.

Villardita, C.; Grioli, S.; Salmeri, G.; Nicoletti, F.; Pennisi, G. 1987. Multicentre clinical trial of brain phosphatidyldserine in elderly patients with intellectual deterioration. Clin Trials J 24(1):84-93.

Wurtman, J.J. 1979. Sources of lecithin and choline in the diet. In: Barbeau, A.; Growdon, J.H.; Wurtman, R.J. (Eds.). Choline and Lecithin in Brain Disorders. Raven Press; New York, Nutrition and the Brain, Vol. 5, pp. 73-81.

Zeisel, S.H.; Garry, P.J.; Brigida, M.; Magil, S.G.; Goodwin, J.S.; Alvarez, N. 1982. Serum choline concentrations in aged humans. In: Corkin, S.; Davis, K.; Growdon, J.; Usdin, E.; Wurtman, R. (Eds.). Alzheimer's Disease: A Report of Progress in Research. Raven Press; New York. Aging Aging, Vol. 19, pp. 45-47.

ATTACHMENT 1

***CURRICULA VITAE* OF EXPERT PANEL MEMBERS**

CURRICULUM VITAE

John Doull, Ph.D., M.D.

OFFICE: University of Kansas Medical Center
Department of Pharmacology, Toxicology and Therapeutics
3901 Rainbow Blvd. Kansas City, KS 66160-7417

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HOME: [redacted]

EDUCATION:

B.S., Chemistry, Montana State College, Bozeman, Mont., 1944
US Navy, Electronics, 1944-1946
Ph.D., Pharmacology, Univ. of Chicago, Chicago, Ill., 1950
M.D., Medicine, Univ. of Chicago, Chicago, Ill., 1953

PROFESSIONAL EXPERIENCE:

University of Chicago Medical School
Research Assistant, Univ. of Chicago Toxicity Laboratory, 1946-1950
Research Associate, US Air Force Radiation Laboratory and Univ. of Chicago Toxicity Laboratory, 1951-1953
Assistant Director, US Air Force Radiation Laboratory & Toxicity Laboratory, 1954-1967
Assistant Professor, Department of Pharmacology, 1956-1957
Associate Professor, Department of Pharmacology, 1957-1967

Pesticides Subcommittee (Chairman), 1975-1977
Committee to Revise Publication 1138, 1976-1977
Chronic Toxicity Subcommittee (Chairman), 1976-1977
Board on Toxicology and Environmental Health Hazards, 1978-1986
Board on Environmental Sciences and Toxicology, 1986-1989
IOM Food Safety Policy Subcommittee, 1978-1979
Committee to study Saccharin and Food Safety Policy, 1978-1979
IOM Advisory Committee on CDC Study of Vietnam Veteran Health, 1985-1988
Committee on Toxicity Testing Strategies (Chairman), 1982-1984
Committee on Mixtures (Chairman), 1986-1988
Committee on Toxicology (Chairman), 1987-1993
Committee on Risk Assessment of Hazardous Air Pollutants, 1990-1993
Committee to Study the Interactions of Drugs, Biologies and Chemicals in Deployed U. S. Military Forces, 1995-1996
Subcommittee on Acute Exposure Guideline Levels, 1997
Board on Environmental Studies and Toxicology 1999
Environmental Protection Agency,Washington, D.C., 1976-1995
FIFRA Science Advisory Panel,. 1976-1980
Worker Re-entry Protocol Group, 1977-1978
Committee on Tolerances, 19.78-1979
Science Advisory Board, Environmental Health Committee, 1980-1989
Organics Subcommittee (Chairman), 1986-1989
Estimating Risks from Dioxins/Dibenzofurans, 1986-1987
Severity of Effects Ranking Schemes, 1985-1986
Acute Toxics Committee, 1996-1987
Hazard Ranking System Committee, 1987-1988
Science Advisory Board, Environmental Health Committee, 1997
Dioxin Reassessment Review Committee 1995
National Institute of Environmental Health Sciences, 1975-1978
NIEHS Advisory Council, 1975-1978
University-Based Centers Subcommittee (Chairman), 1975-1978
Second Task Force on Human Health and the Environment, 1976-1977
Biologic Mechanisms and Toxicity Subcommittee, 1976-1977
F.E.M.A., Washington, D.C., Expert Panel Member, 1977
National Advisory Committee, California Primate Center, Davis, 1977-1980
CPC International, Englewood Cliffs, Toxicology Assessment Group, 1978
Best foods, Union, NJ, Food Safety.and Nutrition Board, 1978-1989

OTA, Wash., Panel on Assessment of Environmental Contaminants, 1978
Rohin and Haas, Philadelphia (Medical Dept), 1980-1989
Stauffer Chemical Corp., Pesticide Advisory Group, 1980-1984
Pillsbury Corp., Minneapolis, 1981.1992
National Toxicology Program, Board of Scientific Counselors Ad Hoc
Panel on Chemical Carcinogenesis Testing & Evaluation, 1982-1984
DIMS Advisory Committee on Long-term Health Effects of Phenoxy
Herbicides and Contaminants, 1982-1985
National Sanitation Foundation, Ann Arbor, 1983-1989
Council of Public Health Consultants, 1983-1989
Health Advisory Board, 1983-19,89
Drinking Water Additives Peer Review Group, 1987-1989
Nutrition Foundation, Washington.
Predictive Role of Mouse Liver Tumors Committee, 1982-1983
UAREP, Panel on Health Aspects of Waste Chemical Disposal, 1983-1984
Kansas Dept. Health and Environment, Topeka, 1983-1987
Toxicology Advisory Committee. 1983-1987
Governors Advisory Committee on Radon (Chairman), 1987-1988
National Institute of Occupational Safety and Health, 1984-1987
Board of Scientific Counselors, 1984-1987
White House Advisory Panel on Ranchhand Veterans, 1984-1986
Clean Sites Inc., Alexandria, Technical Advisory Panel, 1984-1993
Naylor Dana Institute, Advisory Panel on Acetaminophen, 1986-1987
Black and Veatch Engineering Corp., Kansas City, 1986-1987
Denver Water Dept. Reuse Demo. Project Advisory Committee, 1986-1992
Scientific Advisory Panel on Ground Water Recharge (California), 1987
Water Resource Recovery Pilot Plant Project (Tampa, Fl), 1987-1992
Health Effects Group (Chairman), 1987-1992
Monsanto Chemical Corp., St. Louis Alachlor Review Panel, 1987-1988
International Life Sciences Institute, Risk Science Institute, 1988
Armed Forces Epidemiological Board, 1988-1991
Lovelace Biomedical & Environmental Res. Inst. Board of Directors, 1988
Presidential Risk Assessment & Management Commission, 1990-1998
Kansas Governors Surface Water Commission, 1997-1999
Food and Drug Administration, CFSAN Review Panel 1999
Food and Drug Administration, OPS Advisory Committee, 1999-

LOCAL COMMITTEES:

Poison Control Center Committee (Chairman), 1968-1980
Pharmacy and Therapy Committee (Chairman), 1969-1984
Basic Science Lectureship Committee, 1970-1972
Health Care Delivery Systems Committee, 1971-1972
Research Committee, 1971-1973 ~
Animal Care Committee, 1972-1974
Computer Committee (Chairman),.:1972-1974
Search Committee for Chair of Biochemistry, 1975
Search Committee for Dean of School of Nursing (Chairman), 1975
Education Committee, 1976-1977
Faculty Promotion and Tenure Committee, 1976-1977
Curriculum Implementation Committee, 1976
Ad Hoc Ethics Committee, 1976
Long Range Planning Committee, 1976
Information Systems Advisory Committee, 1977
Medical Center Safety Committee (chairman), 1978-1983
    Radiation Safety Committee, 1918-1983
    Biohazards Committee, 1978-1983
    Engineering Safety Committee, 1978-1983
Committee for Intercampus Liaison (Chairman), 1978-1980
Search Committee for Director of Biomedical Engineering (Chairman), 1980
Search Committee for Graduate School Dean (Chairman), 1980
Task Force on Need for School of Public Health, 1980
Education and Curriculum Committee, 1984-1987
Center for Environmental and Occupational Health, 1986
Executive Advisory Committee, 1986-1989
External Advisory Committee, 1986-1989

HONORS/AWARDS:

Sigma Xi (Univ. of Chicago), 1960
Alpha Omega Alpha (Univ. of Kansas), 1973
The Kenneth P. DuBois Award (Midwest Chapter Society of Toxicology), 1985
Samuel Kuna. Award (Rutgers Univ.), 1989
Commander's Award for Public Service (Armed Forces Epidemiological Board), 1990

International Achievement Award (International Society of Regulatory Toxicology), 1990
Ambassador of Toxicology Award (Mid-Atlantic Chapter Society of Toxicology), 1991
Distinguished Medical Alumnus Award (Univ. of Chicago), 1991
Stokinger Award (Amer. Cont. Governmental Industrial Hygienists), 1992
John Doull Award (Mid-America Chapter Society of Toxicology), 1992
Special Recognition Award (University of Kansas Medical Center), 1992
Merit Award (Society of Toxicology), 1993
Snider Award (University of Arkansas Toxicology Symposium Series), 1994
Founders Award (Chemical Industry Institute of Toxicology), 1996
The Meritorious Service Award (Amer. Conf. Gov. Ind. Hygienists), 1996
Honorary Doctor of Pharmacy (The University of Kuopio, Finland), 1996

BOOKS/BOOK CHAPTERS:

Essays in Toxicology (F. Blood, ed.), Academic Press, New York, Effect of Physical Environmental Factors on Drug Response, 1972.

Casarett and Doull's Toxicology: The Basic Science of Poisons, Macmillan Publishing Co., Inc., New York. First Edition (L. J. Casarett and J. Doull, eds.), 1975 Second Edition (C. D. Klaassen, M. 0. Amdur and J. Doull, eds.), 1980 Third Edition (C. D. Klaassen, M. 0. Amdur and J. Doull, eds.), 1986 Fourth Edition (M. 0. Amdur, J. Doull and C. D. Klaassen, eds.), 1991 Fifth Edition (C. D. Klaassen ed., M. 0. Amdur and J. Doull, emeritus eds.) 1995

Insecticide Biochemistry and Physiology (C. Wilkinson, ed.), Plenum Preiss, NY, The Treatment of Insecticide Poisoning, 1976.

Information Technology in Health Science Education (E. Deland, ed.), Plenum Pub. Co., Use of CATS in Pharmacology, 1978.

Food Safety (H. Roberts, ed.), Wiley & Sons, New York, Chapter 7, Food Safety and Toxicology, 1981.

Complex Mixtures, National Academy Press, Washington, D.C., 1988.

Methods to Assess Adverse Effects of Pesticides on Non-target Organism (R. G. Tardiff, ed.), John Wiley & Sons Ltd., Chapter 10, Assessment of Acute
Toxicity of Pesticides on Humans and Domestic Animals, 1992.

Science and Judgement in Risk Assessment, National Academy Press, Washington D. C. 1995

BIBLIOGRAPHY

1. DuBois, K. P, Doull, J., and Coon, J.. M., Toxicity and Mechanism of Action of p-Nitro-phenyl-diethyl-thionophosphate (E605), Proc. 7: 1 (1948).

2. Dubois, K. P., Doull, J., Salerno, P. R., and Coon, I M. Studies on the toxicity and mechanism of action of p-nitrophenyl diethyl thionophosphate (Parathion). J. Pharmacol. Exp. Ther. 95: 79 (1949).

3. DuBois, K. P., Doull, J., and Cochran, K. W. Effects of acute beryllium poisoning on carbohydrate metabolism. Proc. 116th Meeting Amer. Chem. Soc., p. 57 (1949).

4. DuBois, K. P., Doull, J., and Coon, J. M. The cholinergic action of alkyl pyrophosphoramide. J. Pharmacol. Exp. Ther. 98: 6 (1950).

5. Cochran, K. W., Doull, J., Mazur, M., and DuBois, K. P. Acute toxicity of zirconium, columbium, strontium,, lanthanum, cesium, tantalum and yttrium. J. Ind. Hyg. Occup. Med. 1: 637 (1950).

6. DuBois, K. P., Doull, J., and Coon, J. M. Studies on the toxicity and pharmacological actions of octamethyl pyrophosphoramide (OMPA, Pestox 1011). J. Pharmacol. Exp. Ther. 99: 376 (1950).

7. DuBois, K. P., Cochran, K. W., and Doull, J. Inhibition of citric acid synthesis in vitro by x-irradiation. Proc. Soc. Exp. Biol. Med. 76: 422 (1951).

8. Doull, J., DuBois, K. P., and Geiling,:.E. M. K. The biosynthesis of radioactive bufagin. Arch. Int. Pharmacodyn. 86:454 (1951).

9. Doull, J., Hermann, R. G., Geiling E. M. K., and DuBois, K. P. Effects of bufagin on the respiration of cardiac muscle and other tissues. Arch. Int. Pharmacodyn. 86: 487 (1951).

10. Doull, J., and DuBois, K. P. Toxicity and anticholinesterase action of tetra-n-propyl dithionopyrophosphate. J. Pharmacol. Exp. Ther. 106: 382 (1952).

11. DuBois, K. P., Doull, J., Deroin, J., and Cummings, O. K. Studies on the toxicity and mechanism of action of some new insecticidal thionophosphates. Arch. Ind. Hyg. Occup. Med. 8: 350 (1953).

12. DuBois, K. P., Doull, J., Okinaka, A. J., and Coon, J. M. Studies on the toxicity and pharmacological actions of symmetrical and unsymmetrical diethyl bis(dimethylamido) pyrophosphate. J. Pharmacol. Exp. Ther. 107: 464 (1953).

13. Doull, J., and DuBois, K. P. Influence of hibernation on survival time and weight loss of x-irradiated ground squirrels. Proc. Soc. Exp. Biol. Med. 84: 367 (1953).

14. Doull, J. Studies on the cholinesterase activity of tissues of irradiated animals. J. Pharmacol. Exp. Ther. 110: 14 (1954).

15. Okinaka, A. J., Doull, J., Coon, J. M., and DuBois, K. P. Studies on the toxicity and pharmacological actions:of bis(dimethylamido) fluorophosphate (BFP). J. Pharmacol. Exp. Ther. 112:. 231 (1954).

16. Fitch, F. W., Doull, J., and Wissler, R. W. Histopathology of the irradiated hibernating ground squirrel (Citellus tridecemlineatus). AM.A. Arch. Path. 60: 644(1955).

17. Hallesy, D. W., and Doull, J. Acute and chronic toxicity of orange B and orange 1 in rats. J. Pharmacol. Exp. Ther. 116: 26 (1956).

18. Doull, J. Irradiation and survival in hibernating animals. Med. Sci. 1: 27 (1956).

19. Landahl, H. D., Hasegawa, A. T., and Doull, J. Effect of whole body x-irradiation on the heat production and temperature regulation of rats and mice. Radiat. Res. 5: 488 (1956).

20. Doull, J., Plzak, V., and Noble, I F. Synthesis and radioprotective properties of chlorinated O-dialkylaminopropionamideo- and O-dialkylaminopropylaminodiphenyl sulfide derivatives. I Med. Pharm. Chem. 1: 171 (1959).

21. Doull, J., PIzak, V., and Brois, S. I Protective effects of various phenone derivatives against radiation lethality in x-irradiated mice. Radiat. Res. 11: 439 (1959).

22. Noble, J. F., Hasegawa, A. T., Landahl, H. D., and Doull, J. Effect of fractionation on survival of mice following chronic exposure to x-irradiation. Radiat. Res. 11: 457 (1959).

23. Doull, J. Chemical antidotes for radiation injury. Arch. Environ. Health, 2: 284(1961).

24. Vesselinovitch, D., DuBois, K. P., Fitch, F. W., and Doull, I Mammalian toxicity and histopathologic effects of 2,6-dibutyl-4-nitrophenol. Toxicol. Appl. Pharmacol. 3: 713 (1961).

25. Doull, J., Plzak, V., and Root, M. Protection against chronic radiation lethality in mice. Radiat. Res. 16: 578 (1962).

26. Doull, J., Plzak, V., and Brois, S. J. A survey of compounds for radiation protection. USAF School of Aerospace Med. Report, No. 62-29: 1 (1962).

27. Doull, J., Plzak, V., and Root, M. Toxicity and radioprotective activity of p-aminopropiophenone in mice. Radiat. Res. 16: 588 (1962).

28. Plzak, V., and Doull, J Toxicity and radioprotective effects of acetyl p-aminopropiophenone in mice. Radiat. Res. 19: 228 (1963).

29. Oldflield, D. G., Doull, J., Plzak, V., Hasegawa, A., and Sandberg, A. Protection of proton-irradiated mice with p-aminopropiophenone (PAPP) and 2-mercaptoethylamine (MEA). Radiat Res. 19: 229 (1963).

30. Plzak, V., Hasegawa, A. T., and Doull, J. Radioprotective effects of cyclobutane derivatives in mice. Radiat. Res. 22: 224 (1964).

31. Vesselinovitch, D., and Doull, J. Effect of adding Co-ral to the diet of rats and mice. Lab. Anim. Care 14: 325 (1964).

32. Doull, J., Oldfield, D. G., and Plzak, V. Chemical protection against high energy proton radiation in mice. Blood, The Journal of Hematology 24: 638 (1964).

33. Oldfield, D. G., Doull, J., and Plzak, V. Chemical protection against 440 Mev protons in mice treated with mercaptoethylamine (MEA) or p-aminopropiophenone (PAPP). Radiat. Res. 26: 12 (1965).

34. Oldfield, D. G., Doull, J., and Plzak, V. Chemical protection against absorber moderated protons. Radiat. Res. 26: 25 (1965).

35. Plzak, V., and Doull, J. Dose reduction factors (DRF) for various radioprotective agents in mice. Radiat. Res. 25: 228 (1965).

36. Plzak, V., and DouU, J. Comparative subacute oral toxicity of some organic phosphates in rats and dogs. Toxicol. Appl. Pharmacol. 8: 350 (1966).

37. Goepp, R. A., Fitch, F. W., and Doull, J. The use of parenteral chemical for protection against oral radiation death in mice. Radiat. Res. 31: 149 (1967).

38. Doull, J. Pharmacologic responses in irradiated animals. Radiat. Res. 30: 333(1967).

39. Plzak, V., and Doull, J. A further survey of compounds for radiation protection. USAF School of Aerospace Med. Report, #SAM TR 69-1: 1 (1969).

40 Doull, J., et. al., Guidelines for estimating toxicologically insignificant levels of chemicals in food, Report of the Food Protection Committee, Food Nutrition Board, Nat. Res. Council/National Acad. Sci., Nat Acad. Press, Washington, D. C., (1969)

41. Goldstein, G. M., and Doull, J. Treatment of nitrite-induced methemoglobinemia with hyperbaric oxygen. Proc. Soc. Exp. Biol. Med., 138: 137(1971).

42. DeFeo, F. G., Fitzgerald, T. J., and. Doull, J. Synthesis and biologic activity of p-hydroxylaminopropiophenone. J. Med. Chem. 15: 1185 (1972). 43. Doull, I The effect of physical environmental factors on drug response. In Essays in Toxicology (W. J. Hayes, ed.), Chapter 2, Academic Press, New York, N.Y. (1972).

44. Goldstein, G. M., and Doull, J., The use of hyperbaric oxygen in the treatment of p-aminopropiophenone-induced methemoglobinemia. Tox. Appl. Pharm., 26: 247 (1973)

45. Fitzgerald, T. J., Doull, J., and DeFeo, F. G. Radioprotective activity of p-aminopropiophenone: Structure activity relationships. Rad. Res. 55: 3 (1973).

46. Hurwitz, A., and Doull, J. Effect of irradiation on gastrointestinal drug absorption. Radiat. Res. 59: 606 (1974).

47. Doull, J. Factors influencing toxicity. In Casarett and Doull's Toxicology: The Basic Science of Poisons (J. Doull and L. J. Casarett, eds.), Chapter 5, Macmillan Publishing Co., Inc., N.Y. (1975).

48. Doull, J., and Casarett, L. J. (eds.). Casarett and Doull's Toxicology: The Basic Science of Poisons, Macmillan Publishing Co., Inc., N.Y. (1975).

49. Doull, J. Evaluation of the toxicity of food additives. Proc. Sixth Internat. Congress of Pharmacol. 6: 115 (1975).

50. Doull, J. Pesticide-induced delayed neurotoxicity. In Pesticide Induced Delayed Neurotoxicity (R. L. Baron, ed.), EPA 600/1-76-025, Chapter 8, Washington, D.C. (1976).

51. Doull, J. The treatment of insecticide poisoning. In Insecticide Biochemistry and Physiology (C. A. Wilkerson, ed.), Chapter 16, Plenum Press, New York, N.Y.(1976).

52. Doull, J., and Walaszek, E. J. The use of Computer Assisted Teaching Systems in Pharmacology. In Computers in Medical Education (E. DeLand, ed.), Chapter 12, Plenum Pub. Co., New York, N.Y. (1977).

53. Doull, J., Clinical toxicology aspects of controlled release pesticide formulations. ACS Symposia Series, Herbert Scher Ed., 53: 54 (1977)

54. Nelson, S. R., Doull, J., Tockman, B. A., Cristiano, P.J., and Samson, F. E., Regional brain metabolism changes induced by acetylcholinesterase inhibitors, Brain Research, 157: 186 (1978)

55. Doull, J., Klaassen, C. D., and Amdur, M. 0. (eds.). Casarett and Doull's Toicology: The Basic Science of Poisons, 2nd Ed., Macmillan Publishing Co., Inc., N.Y. (1980).

56. Klaassen, C. D., and Doull, J. Evaluation of safety: toxicologic evaluation. In Casarett and Doull's Toxicology: The Basic Science of Poisons (J. Doull, C. D. Klaassen and M. Amdur, eds.), pp. 28-55, Macmillan Publishing Co., Inc., N.Y.(1980).

57. Misawa, M., Doull, J., Kitos, P. A., and Uyeki, E. M. Teratogenic effects of cholinergic insecticides in chick embryos. 1. Diazinon treatment on acetylcholinesterase and choline acetyltransferase activities. Toxicol. Appl. Pharmacol. 57: 20-29 (1981).

58. Misawa, M., Doull, J., and Uyeld, E. M. Mechanisms of teratology induced by organophosphates. 8th Int. Congress of Pharmacology, July 19-24, Tokyo, Japan (1981). (Abst.)

59. Eigenberg, D., Pazdernik, T., and Doull, J. Hemoperfusion: a possible alternative method for treating organophosphate insecticide poisoning. The Toxicologist 1: 136 (1981).

60. Doull, J., Food safety and toxicology, in Food Safety, H. R. Roberts Ed., Chapter 7: 295 (1981).

61. Misawa, M., Doull, J., and Uyeki,, E., Teratogenic effects of cholinergic insecticides in chick embryos, III Development of cartilage and bone, Jour. Tox. and Env. Health 10: 551 (1982)

62. Doull, J. Assessing pesticide toxicity in man and correlations with laboratory animal studies. In J. Miyamoto et al. (ed.). IUPAC Pesticide Chemistry, Kyoto, Japan, Pergamon Press (1983).

63. Eiginberg, D. A., Pazdernik, T. L., and Doull, J., Hemoperfusion and pharmacokinetic studies with methamidophos in the rat, Fund. Appl. Tox 3: 496 (1983).

64. Doull, J (Chair). et. al., The relevance of mouse liver hepatoma to human carcinogenic risk, Report of an international expert committee to The Nutrition Foundation, September (1983).

65. Doull, J. The past, present and future of toxicology. Pharm. Rev. 36: 15S-18S (1984).

66. Doull, J (chair) et. al., Report of the NTP ad hoc panel on chemical carcinogenesis testing and evaluation, Report to the Board of Scientific Councelors of the National Toxicology Program, (1984).

67. Doull, J. (co-chair) et. al., Toxicity testing; Part 2, strategies to determine needs and priorities, Nat. Acad. Press., Washington, D.C., (1984).

68. Doull, J., NTP Blue Ribbon Panel. Report; Report from the chairman, Toxicology Forum.,

68. Klaassen, C. D., Amdur, M. O., and Doull, J. (eds.). Casarett and Doull's Toxicology: The Basic Science of Poisons, 3rd Ed., Macmillan Publishing Co., Inc., N.Y. (1986).

69. Doull, J., Introduction to Toxic Substances and Human Risk, Tardiff, R. G., and Rodricks, J. V., Eds., pp 3, Plenum Publishing Co., Inc. (1987)

70. Doull, J., and Bruce, M. C. Origin and scope of toxicology. In Casarett and Doull's Toxicology: The Basic Science of Poisons (C. D. Klaassen, M. 0. Amdur and J. Doull, eds.), pp. 3-10, Macmillan Publishing Co., Inc., N.Y. (1986).

71. Doull, J., The mouse in safety evaluation, Arch. Tox. Suppl. 10: 3 (1987).

72. Doull, J.(Chair), Complex Mixtures, Committee on Methods for the In Vivo Toxicity Testing of Complex Mixtures, National Research Council, National Academy of Sciences, National Academy Press, Wash. D. C., (1988).

73. Doull, J., Understanding Risk, Scientific Sources of Confusion, Health and Environment Digest 4: No. 2,3-5 (1990).

74. Wood, L. A., and Doull, J. Gras evaluation of flavoring substances by the expert panel of FEMA. Reg. Tox. Pharm. 14: 48-58 (1991).

75. Amdur, M. O., Doull, J. and Klaassen, C. D. (eds), Casarett and Doull's Toxicology: The Basic Science of Poisons, 4th Ed., Pergamon Press, Inc., New York, (1991).

76. Gallo, M. and Doull, J. History and Scope of Toxicology, in Casarett and Doull's Toxicology: The Basic Science of Poisons (Amdur, M. O., Doull, J. and Klaassen, C. D. eds), pp 3-11, Pergamon Press Inc., New York, (1991).

77. Levine, R. S. and Doull, J. Global estimates of acute pesticide morbidity of mortality. Rev. Env. Contam. and Toxicol.: 129,29-50 (1992).

78. Doull, J. Toxicology and exposure limits. Appl. Occup. Environ. Hyg. 7: 583-585 (1992).

79. Doull, J. Assessment of acute toxicity of pesticides on humans and domestic animals. In Methods to Assess Adverse Effects of Pesticides on Non-target Organisms (R. G. Tardiff, ed.), Chapter 10, John Wiley & Sons Ltd., West Sussex, England (1992).

80. Waddell, W. J., Borzelleca, J. F., Doull, J., Grasso, P, LeBourhis, B., Levy, P. S., and Tamburo, C. H., Alcohol and Cancer, Br. J. Cancer: 66,1200 (1992).

81. Doull, J., Hazard and dose response assessment, Conference on the risk assessment paradigm after 10 years., Wright Patterson, OH, April 5-8 (1993).

82. Rozman, K., Roth, W. L., Greim, H., Stahl, B. U. and Doull, J. Relative potency of chlorinated dibenzo-p-dioxins (CDDs) in acute, subchronic and chronic (carcinogenicity) toxicity studies: implications for risk assessment of chemical mixtures. Toxicology 77: 39-50 (1993).

83. Zapp, J. A., and Doull, J., Industrial Toxicology: Retrospect and Prospect, in Patty's Industrial Hygiene and Toxicology, Clayton G. D., and Clayton, F. E., Eds. Chap. I Vol. 2, Part 1: 1 (1993)

84. Doull, J., Principles of risk assessment: Overview of the risk assessment process, Proceeding of Conf. on Chemical Risk Assessment in the DoD, Science, Policy and Practice, A.L-TR-1993-001,: NMRI-93-10, (1993)

85. Andersen, R.A., Colton, T., Doull, J., Marks, J. G., and Smith, R. G., Designing a biological monitoring program to assess community exposure to chromium: Conclusions of an Expert Panel, J. Tox. Env. Health 40: 555 (1993).

86. Munro, I. et. al., Interpretive Review of the Potential Adverse Effects. of Chlorinated Organic Chemicals on Human Health and the Environment; Report of an Expert Panel. Reg. Toxicology. and Pharmacology, 20: part 2, 1-1056 (1994).

87. Doull, J., The ACGIH approach and practice, Appl. Occup. Environ. Hyg., 9(1): 23 (1994).

88. Craun, G. F., Bull, R. J., Clark, R. M., Doull, J., Grabow, W., Marsh, G. M., Okun, D. A., Regli, S., Sobsey, M. D., and Symonds, J. M., Balancing chemical and microbial risks of drinking water; Part 1, Benefits and potential risks, J. Water SRT 43 #4: p 193 (1994)

89. Craun. G. F., Bull, R. J., Clark, R. M., Doull, J., Grabow, W., Marsh, G. M., Okun, D. A., Regli, S., Sobsey, M. D., and Symonds, J. M., Balancing chemical and microbial risks of drinking water; Part 2, Managing the risks, J Water SRT 43 #5: p207 (1994).

90. Doull, J., et. al., Science and Judgement in Risk Assessment, National Academy Press, (1994)

91. Doull, J., Chlorinated organic chemicals: Occupational aspects, Toxicology Forum., Berlin Germany. Sept. 19-21 (1994)

92. Doull, J., Recommended Limits for Exposure to Chemicals, in Casarett and Doull's Toxicology: The Basic Science of Poisons, 5th Ed., Klaassen, C. D. ed, Appendix A, McGraw-Hill, New York, NY (1995).

93. Neal, R. A., and Doull, J., Commentary: The Discipline of Toxicology, Fundamental and Applied Toxicology 24: 5-7 (1995)

94. Doull, J., Keynote Address: Improving the science and art of risk assessment, Drug Metabolism Reviews: 28 (1&2) (1996)

95. Rozman, K., Kerecen, L., Viluksela, M. K., Osterle, D., Deml, E., Vilukseal,. M., Stahl, B., U., Greim, H., and Doull, J., A toxicologist's view of cancer risk assessment, Drug Metabolism Reviews:28 (1&2), 28-52, (1996)

96. Doull, J., Rozman, K. K., and Lowe, M. C., Hazard evaluation in risk assessment: What ever happened to sound scientific judgement and weight of evidence?, Drug Metabolism Reviews:28 (1&2), (1996)

97. Doull, J., Toxicology in the 21st Century, Science (Kexue): 48 No. 2, 14-16 (1996)

98. Doull, J., Is it Safe?, CIIT Founder's Award Address, CIIT Activities, Vol 16, May (1996)

99. Omenn, G. S., Kessler, A. C., Anderson, N. T., Chiu, P., Doull, J., Goldstein, B., Lederberg, J., McGuire, S., Rall, D., Weldon, V. V., Risk Assessment and Risk Management in Regulatory Decision-Making, Draft Report of the Commission on Risk Assessment and Risk Management, June (1996)

100. Smith, R. L., Newberne, P., Adams., T. B., Ford, R. A., Hallagan, J. B., and The Fema Expert Panel, Recent Progress in Consideration of Flavour Ingredients Under the Food Additive Ammendments 17, Gras Substances.

101. Adams, T. B., Doull, J., Goodman, J. I., Munro, I. C., Newbern, P., Portoghese, P. S., Smith, R. L., Wagner, B. M., Weil, C. S., Woods, L. A., and Ford, R. A., The FEMA GRAS Assessment of Furfural Used as a Flavor Ingredient.

102. Doull, J., Specificity and Dosimetry of Toxicologic Responses, Reg. Tox and Pharm., 24, (1996).

CURRICULUM VITAE

EARLE R. NESTMANN

EDUCATION

1974	Ph.D., Biology (Genetic Control of Mutagenesis), York University, Toronto, Ontario.
1971	M.Sc., Biology (Genetics of DNA Repair in Bacteria), York University, Toronto, Ontario.
1968	B.Sc., Biology (Vertebrate Zoology), Marietta College, Ohio, U.S.A.

EMPLOYMENT HISTORY

1999-Present	**CANTOX HEALTH SCIENCES INTERNATIONAL**, Mississauga, Ontario Principal and Vice President
1988-1999	**CanTox, Inc.**, Consultants in Health and Environmental Sciences, Mississauga, Ontario. Principal and Vice President.
1986-1987	**Cyanamid Canada Inc.**, Research and Development, Crop Protection Division, Toronto. Manager, Regulatory and Environmental Affairs.
1977-1986	**Department of National Health & Welfare**, Health Protection Branch, Ottawa, Ontario. Mutagenesis Section, Research Scientist.
1974-1977	**York University**, Department of Biology, Toronto, Ontario. Visiting Assistant Professor.

PROFESSIONAL ACTIVITIES

1999-Present	Member, Board of Trustees, American Type Culture Collection (ATCC)
1998-2001	Member, Board of Directors, Cantox Environmental Inc.
1993-2001	Member, Board of Scientific Directors, American Type Culture Collection (ATCC)
1995-1999	Member, Royal Society of Canada Committee on Expert Panels
1995-1996	Member, Board of Directors, CENSOL Inc. (Canadian Environmental Solutions)
1994-1995	Member, Ontario Biotechnology Advisory Board
1989-1991	President, Genetics Society of Canada
1982-1991	Member, Review Panels on *Salmonella* Testing, National Toxicology Program, U.S. Department of Health and Human Services
1989-1990	Member, Peer Review Panel, Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Ethylbenzene
1988-1989	Member, Advisory Committee, Canadian Soft Drink Association
1988	Local Arrangements Committee, XVI International Congress of Genetics, Toronto
1982-1994	Editorial Board, Mutation Research
1986-1994	Editorial Board, Environmental and Molecular Mutagenesis
1980-1993	Associate Editor, GENOME

1986	Chairman, National Committee, 13th International Conference on Yeast Genetics and Molecular Biology, Banff
1985-1987	Member, Subcommittee on Disinfectants of the Safe Drinking Water Committee of the U.S. National Academy of Sciences
1985-1994	Member, Committees for the International Conferences on Mechanisms of Antimutagenesis and Anticarcinogenesis
1983-1987	Member, ASTM Task Force on the Ames Assay for Committee E47/0.9 on Genetic Toxicology
1983-1984	Member, Department of National Health and Welfare, Health Protection Branch Science Panel on Toxicology and Pathology
1982-1985	Member, Biochemical Technology Advisory Committee, Algonquin College Ottawa
1982	Member, Advisory Committee on Biotechnology, Ottawa-Carleton Training Council
1981-1984	Advisory Committee on Environmental Mutagenesis, Joint Ministerial Committee for the Department of National Health and Welfare and the Department of Environment – member of Secretariat
1981-1984	Member, Advisory Panel, Strategic Grants in Environmental Toxicology, Natural Sciences and Engineering Research Council of Canada
1980	Chairman, Local Organizing Committee for the International Symposium on Chemical Mutagenesis, Human Population Monitoring, and Genetic Risk Assessment, Ottawa

Books, Monographs

Nestmann, E.R. (Ed.) 1991. Special Issue. Recommended Protocols Based on a Survey of Current Practice in Genotoxicity Testing Laboratories. Mutat Res 246(No.2):227-330.

Nestmann, E.R. 1986. Guidelines on the Use of Mutagenicity Tests in the Toxicological Evaluation of Chemicals, published by Health and Welfare Canada and by Environment Canada, 1986, 84 pp. as part of the Secretariat for the Department of National Health and Welfare and the Department of Environment, Environmental Contaminants Advisory Committee on Mutagenesis. Also published in Environ. Molec Mutag 11(1988):261-304.

Dillon, J.R., Nasim, A., and Nestmann, E.R. 1985. Recombinant DNA Methodology: A Laboratory Manual, John Wiley & Sons, pp. 219.

Bora, K.C., Douglas, G.R., and Nestmann, E.R. (Eds.) 1982. Progress in Mutation Research, Vol. 3: Proceedings of the International Symposium on Chemical Mutagenesis, Human Population Monitoring, and Genetic Risk Assessment, Elsevier/North-Holland Press, pp. 364.

CANTOX Reports (Selected Examples)

(Numerous unpublished reports on genetic toxicology, toxicology, biotechnology, risk assessment, *etc.* Prepared on behalf of CANTOX for various clients.)

Toxicology Reviews: (Confidential) New Drug Submissions

Report of an Expert Panel. Interpretive Review of the Potential Adverse Effects of Chlorinated Organic Chemicals On Human Health and The Environment.

Assessment of Risks Associated with the Domestic Use of (Confidential) for the Treatment of Drinking Water.

(Confidential): Significant Considerations for Product Registration.

Results of the Sampling Program for the Determination of Lead Content in Dust and Soil in the (Confidential) Area.

Compilation and Review of Practices and/or Information Relating to the Uses and Manufacturing Methods for Microorganisms in Biotechnology Products Subject to the Canadian Environmental Protection Act (CEPA).

Compilation and Review of Practices and/or Information Relating to the Risk Assessment of Environmental Introduction of Protozoa and Algae in Biotechnology Products Subject to the Canadian Environmental Protection Act (CEPA).

The Evaluation of the Cardiotoxic Potential of the Two Candidate Anti-Emetic Drugs.

Health Risk Assessment of Soil and Water Contaminants in the Vicinity of a former Gas Station.

Toxicological Evaluation of an Antiemetic Agent.

Assessment of the Potential Risks Associated With The Use of Biological Agents (Natural or Modified) in the Workplace.

A Biotechnology Directory for Atlantic Canada Subject to Regulations Development Under The Provisions of the Canadian Environmental Protection Act (CEPA).

Review of Information Related to Recommended Exposure Limits for Electromagnetic Fields.

An Overview of the Associated Costs of Toxicity Testing of Microbial Products for Compliance with Schedule XV of the Proposed CEPA Regulations, Environment Canada.

Potential Adverse Health Effects Associated with Indoor Air Contaminants.

WHMIS Classification of Fly Ash.

Environmental Risk Assessment of Fluoride.

Health Risk Assessment of a PCB/Hazardous Waste Incineration Site to be Located in Swan Hills, Alberta.

Assessment of the Possible Carcinogenicity of HI-6.

Health Hazard Evaluation of Emissions Resulting from the Destruction of PCB by Incineration, Smithville, Ontario.

Health Hazard Evaluation of Emissions Resulting from the Destruction of Vesicant Warfare Agents, Mustard Gas and Lewisite by Incineration, Suffield, Alberta.

Health Hazard Evaluation of Emissions Resulting from the Destruction of PCB by Incineration, CFB, Goose Bay, Labrador.

Publications/Presentations:

Lee-Brotherton, V., Lynch, B., Musa-Veloso, K., Goodfellow, G., Cheng, E., Haighton, L., and Nestmann, E. 2005. Safety assessment and risk/benefit analysis of the use of azodicarbonamide in baby food jar closure technology: Putting trace levels of semicarbazide exposure into perspective. Annual Meeting of the Society of Toxicology, March 2005. (Abstract 1408)

Nestmann, E.R. 2005. Letter to the Editor. Lead chromate. Mutation Research: Genetic Toxicology and Environmental Mutagensis. In press.

Nestmann, E.R., Lynch, B.S., and Ratpan, F. 2005. Perspectives on the Genotoxic Risk of Styrene. J Toxicol Environ Health B(8):95-107.

Nestmann, E.R., Haighton, L.A., Cheng, E., and Halford, R.A. 2004. A Critical Look at the European Union Drinking Water Parametric Value and its Misapplication as an Indicator of Health Risk. Toxicological Sciences (abstract 1806). Presented at SOT 2004 Annual Meeting.

Nestmann, E.R. 2004. Canadian natural health products (NHP) regulations. Presented at: WORLDNUTRA Conference and Exhibition. November 8, 2004

Nestmann, E. R. 2003. Safety evaluation of dietary supplement ingredients and products. Presented at: SupplySide West Education Session, October 1, 2003

Nestmann, E.R. 2003. Trace level safety assessment process for biotechnology-derived material in seed, food and feed. Presented at: Trace Level Assessment Workshop. Rideau Room, Sheraton Hotel, Ottawa. April 24th, 2003

Nestmann, E.R., Lee-Brotherton, V. and Haighton, L. 2003. Identifying potential risks of hepatoxicity associated with botanical dietary supplements prior to marketing. Presented at Hepatoxicity Assessment for Botanical Dietary Supplements. Bethesda, Maryland, September 8-9.

Goodfellow, G., Lee-Brotherton, V., Daniels, J., Roberts, A, and Nestmann, E. 2003. Antibacterial resistance and triclosan. Toxicological Sciences (abstract 1470).

Nestmann, E.R., Lynch, B.S., and Ratpan, F. 2003. Evaluation of the genotoxic potential of styrene. 2003 Society of Toxicology Meeting. Toxicological Sciences (abstract 683).

Nestmann, E., Copeland, T., and Hlywka, J. 2002. The regulatory and science based evaluation of genetically modified food crops: A USA perspective. In: Atherton, K. (Ed.) Genetically Modified Crops: Assessing Safety. Taylor & Francis; New York. 10:56:53

Nestmann, E., Tai, V., and Daniels, J. 2002. Safety evaluation of ephedra dietary supplements. Toxicological Sciences (abstract 929).

Manley, J., Tai, V., Luksic, M., Mitchell, J., Daniels, J., and Nestmann, E.R. 2001. Maximizing the Chances of Success for New Products Being Developed by Small and Virtual Biotechnology Companies. Pharma, Biopharma & Nutraceuticals Canada. 2001:14-19.

Manley, J.J., Tai, V.M., Lee-Brotherton, V., Luksic, M.C., Nestmann, E.R., and Daniels, J.M. 2001. Renal effects of the peptide bombesin. Toxicological Sciences (abstract 1477).

Davies, T.S., Lynch, B.S., Monro. A.M., Munro, I.C., and Nestmann, E.R. 2000. Rodent carcinogenicity tests need to be no longer than 18 months: An analysis based on 210 chemicals in the IARC monographs. Food Chem Toxicol 38(2-3):219-235.kl

Manley, J. and Nestmann, E.R. 2000. The Regulation and Control of Food and Drugs in Canada: Legislation and Regulations - Part II - Drugs. University of Toronto, September 19, 2000, Toronto, Ontario.

Daniels, J.M., Mitchell, J., and Nestmann, E.R. 2000. Creating value for small and virtual companies through rapid entry into clinical trials. Toronto, Ontario, June 6-7, 2000.

Daniels, J.M., Luksic, M., and Tai, V. 2000. Preclinical development programs for small and virtual companies. J Pharm Pharmaceut Sci 3(1):173.

Tai, V.M., Mitchell, E.J., Lee-Brotherton, V., Manley, J., Nestmann, E.R., and Daniels, J.M. 2000. Safety evaluation of intravenous glycine in formulation development. J Pharm Pharmaceut Sci 3(1):198.

Manley, J., Lee-Brotherton, V., Tai, V., Luksic, M., Mitchell, J., Daniels, J., and Nestmann, E.R. 2000. Creating Value for Small and Virtual Companies Through Rapid Entry into Clinical Trials. [abstract] Biofuture 2000, September 11-13, Calgary, Alberta.

Nestmann, E.R. 2000. Perspective on Risk Assessment of Cry9C Protein in StarLink Corn and on Adverse Event Reporting. Presentation to the FIFRA Scientific Advisory Panel (SAP). Open Meeting, November 28, 2000, Arlington, Virginia.

Nestmann, E.R. 2000. Mode of Action for Atrazine: An Assessment and Review of the EPA Position. June 27.

Nestmann, E.R. 2000. Relevance to Humans of the Mode of Action Associated with Mammary Gland Tumor Development in Atrazine-Treated Female Sprague-Dawley Rats: An Assessment and Review of The EPA Position. January 27.

Nestmann, E.R., and Haighton, L. 2000. Critique of Pesticides: "Making the Right Choice for the Protection of Health and the Environment": The CACCIA Report. September 14, Ottawa, Ontario.

Daniels, J.M., Tai, V.M., Mitchell, E.J., Rose, R, and Nestmann, E.R. 2000. Safety evaluation of intravenous glycine. Toxicological Sciences 54:396 (abstract 1858).

Tai, V.M., Mitchell, E.J., Lee-Brotherton, V., Manley, J., Nestmann, E.R., and Daniels, J.M. 2000. Safety evaluation of intravenous glycine in formulation development. J Pharm Pharmaceut Sci 3(1):156-218.

Lynch, B.S., Capen, C.C., Nestmann, E.R., Veenstra, G., and Deyo, J.A. 2000. Comment: Reply to comment on subchronic /chronic toxicity of antimony potassium tartrate (APT) Regul Toxicol Pharmacol 32:339-340.

Davies, T.S., Lynch, B.S., Monro, A.M., Munro, I.C., and Nestmann, E.R. 1999. Rodent carcinogenicity tests need be no longer than 18 months; an analysis based on 210 chemicals in the IARC Monographs. Food Chem Toxicol 38:219-235.

Munro, I.C., Delzell, E.S., Nestmann, E.R., and Lynch, B.S. 1999. Viadent usage and oral leukoplakia: A spurious association. Regul Toxicol Pharmacol 30(3):182-196.

Lynch, B.S., Capen, C.C., Nestmann, E.R., Veenstra, G., and Deyo, J.A. 1999. Review of subchronic /chronic toxicity of antimony potassium tartrate (APT). Regul Toxicol Pharmacol 30(1):9-17.

Sherman, J.H., Nair, R.S., Steinmetz, K.L, Mirsalis, J.C., Nestmann, E.R., and Barter, J.A. 1999. Evaluation of unscheduled DNA synthesis (UDS) and replicative DNA synthesis (RDS) following treatment of rats and mice with p-dichlorobenzene. Teratogen Carcin Mut 18:309-318.

Daniels, J.M., Nestmann, E.R., Ridley, D., Kerr, A.B., and Rose, R. 1999. Aluminum: An assessment of its possible association with the development of Alzheimer's disease. Annual Scientific Conference of the Cosmetic, Toiletry, and Fragrance Association (CTFA), November 1999.

Kerr, A.B., Rose, R.J., Daniels, J.M., and Nestmann, E.R. 1999. Aluminum: An assessment of its possible association with the development of Alzheimer's disease. Toxicological Sciences 43 (abstract 380).

Copeland, T., Nestmann, E.R., McColl, D., and Schinkel, H. 1999. Managing North American and European scientific and regulatory consideration for the commercialization of genetically modified foods and processes. Molecular Farming Conference.

Nestmann, E., Monro, A., Davies, T., Lynch, B., and Munro, I. 1998. Rodent cancer bioassays could be terminated at 18 months. Abstract submitted for 1999 Society of Toxicology Meeting. Toxicological Sciences (abstract 1594).

Wilson, R., Daniels, J., Nestmann, E., Lynch, B., Hinberg, I., Daka, J., and Rocheleau, M.J. 1998. Application of Risk Assessment Methodology to the Characterization of Degradation Products of Medical Device Materials. Proc Soc Toxicol Pathol, 17:P23.

Daniels, J.M., Copeland, T., and Nestmann, E.R. 1998. Status Report of the ICH Guidelines Relating to the Preclinical Safety Evaluation of New Biopharmaceuticals. Biotechnology Focus 1:7-8 (March 1998).

Daka, J., Hinberg, I., Rocheleau, M.J., Daniels, J.M., Nestmann, E., Lynch, B., and Wilson, R. 1998. Quantitative risk assessment of 4,4'-methylenedianiline released from nasogastric feeding tubes and haemodialyzers. Proc Can Biomat Conf, 1998.

Davies, T.S., Monro, A.M., Lynch, B.S., Munro, I.C., and Nestmann, E.R. 1998. Rodent cancer bioassays should be terminated at 18 months. International Centre of Toxicology (Paris).

Lynch, B., Daniels, J., Nestmann, E., Wilson, R., Munro, I., Sharma, R., Grabarz, R., Dressler, W., Cowsar, D., Gettings, S., Goldberg, M., Haining, L., Herrera, J. Herrera, Kambe, T, McEwen, G., Meltzer, N., Penicnak, A. J., Pennisi, S., and Schwartz, I. 1998. Assessment of the reproductive risks posed to hairdressers and consumers exposed to hair dye products containing p-aminophenol. Annual Scientific Conference of the Cosmetic, Toiletry, and Fragrance Association (CTFA), November 1998.

Nestmann, E.R., and Daniels, J.M. 1998. Company-sponsored expert panel reviews of New Drug Submissions. Meeting of the Montréal Pharmaceutical Discussion Group, Phoenix International Life Sciences, Montréal, Québec, September 30, 1998.

Davies, T.S., Monro, A.M., Lynch, B.S., Munro, I.C., and Nestmann, E.R. 1998. Rodent cancer bioassays should be terminated at 18 months. International Centre of Toxicology (Paris).

Bryant, D., Daniels, J., Lynch, B., Nestmann, E., and Ridley, D. 1998. Evaluation of genotoxic potential of phenolphthalein in mechanistic studies using the transgenic mouse p53 +/- alternative model. Environ Mutagen Society 31(Suppl 29):T46.

Bryant, D., Daniels, J., Lynch, B., Nestmann, E., and Ridley, D. 1998. Interpretation of the data related to the mutagenic/genotoxic potential of phenolphthalein. Toxicologist 42(1S):1119.

Bryant, D., Daniels, J., Lynch, B., Nestmann, E., and Ridley, D. 1998. Evaluation of genotoxic potential of phenolphthalein in mechanistic studies using the transgenic mouse p53 +/- alternative model. Proc Soc Toxicol Pathol 17:P22.

Lynch, B., Daniels, J., Nestmann, E., Wilson, R., Munro, I., Sharma, R., and Dressler, W. 1998. Assessment of the reproductive risks posed to hairdressers and consumers exposed to hair dye products containing *p*-aminophenol. Toxicologist 42(1S):1107.

Nestmann, E., Lynch, B., Wilson, R., Daniels, J., Hinberg, I., Daka, J., and Rocheleau, M.J. 1997. A case study in biomaterials risk assessment: the release of 4,4' methylenedianiline (MDA) from certain polyurethane medical devices. Toxicologist 36(1):172 (abstract 875).

Daniels, J.M., and Nestmann, E.R. 1997. Company-sponsored expert panel reviews of New Drug Submissions: an opportunity for industry. Published in *The N.O.C.*, an official publication of the Canadian Association of Pharmaceutical Regulatory Affairs, March 1997, Pages 1-4.

Daniels, J.M., Kerr, A., and Nestmann, E.R. 1997. Development of stereoisomeric (chiral) drugs: A brief review of scientific and regulatory considerations. Drug Inf J 3:639-646.

Daniels, J., Feniak, A., and Nestmann, E. Assessment of decabromodiphenyl oxide (DBDPO) as a contaminant in the manufacture of a drug substance. Society of Toxicology Annual Meeting, March 9-13, 1997, Cincinnati, Ohio. Abstract No. 1389. The Toxicologist 36(1, Part 2):273-274.

Nestmann, E.R. 1996. Executive Summary. Workshop: The toxicological significance of DNA adducts. Reg Toxicol Pharmacol 23:1.

Munro, I.C., McGirr, L.G., Nestmann, E.R., and Kille, J.W. 1996. Alternative Approaches to the Safety Assessment of Macronutrient Substitutes. Reg Toxicol Pharmacol 23:S6-S14.

Nestmann, E., Lynch, B., Wilson, R., Daniels, J., Hinberg, I., Daka, J., and Rocheleau, J.M. 1996. Human health risk assessment of 4,4'-methylenedianiline (MDA) released from certain polyurethane medical devices. Proceedings of the 5th World Biomaterials Congress II-527, Toronto, Ontario, May 28-June 2, 1996.

Munro, I.C., Lynch, B.S., Kittur, A., and Nestmann, E.R. 1995. Modulators of carcinogenesis. Reg Toxicol Pharmacol 21:60-70.

Daniels, J.M., Kerr, A., and Nestmann, E.R. 1995. Scientific and Regulatory Considerations for the Development of Stereoisomers (Chiral) Drugs. Published in the Summer 1995 edition of *The N.O.C.*, an official publication of the Canadian Association of Pharmaceutical Regulatory Affairs.

Daniels, J.M., Levins, K.M., Kille, J.W., Nestmann, E.R., and Munro, I.C. 1995. The Drugs Directorate of the Canadian Health Protection Branch: A Brief Overview. Soteros Bulletin, Issue 6, Pages 8-12.

Blakey, D.H., Maus, K.L., Bell, R., Bayley, J., Douglas, G.R., and Nestmann, E.R. 1994. Mutagenic Activity of 3 Industrial Chemicals in a Battery of *In Vitro* and *In Vivo* Tests. Mutat Res 320:273-283.

Nestmann, E.R., Gowdy, K.M., Roest, N.M., and Reeve, D.W. 1994. The Safety of Chlorine Bleached Paper Products. Pulp and Paper Canada, 95:133-136.

Daniels, J.M., Willes, R.F., and Nestmann, E.R. 1994. Polyvinyl Chloride. Contributing authors to Synthetic Polymers (Chapter 37), Harris, L.R., and Sarvadi, D.G. In: Clayton, G.D., and Clayton, F.E. (Eds.) Patty's Industrial Hygiene and Toxicology, Fourth Edition, Volume 2, Part E (Toxicology). John Wiley & Sons Inc., New York, NY.

Levins, K.M., Daniels, J.M., Lynch, B.S., Davies, D.B., and Nestmann, E.R. 1994. Section 17 of the Canadian Environmental Protection Act: What's In It For The Pharmaceutical Industry? Published in the December 1994 edition of *The N.O.C.*, an official publication of the Canadian Association of Pharmaceutical Regulatory Affairs.

Munro, I.C., McGirr, L.G., Nestmann, E.R., and Kille, J.W. 1994. Safety Factor Alternatives and Human Mimetic Models. Presented at Society of Toxicology 1994 Annual Meeting March 13-17.

Munro, I.C., McGirr, L.G., and Nestmann, E.R. 1994. Alternatives to Traditional Safety Testing. Symposium: Approval of Macronutrient Substitutes: Overcoming the Obstacles. Presented at IFT Annual Meeting June 26.

Willes, R.F., Nestmann, E.R., Miller, P.A., Orr, J.C., and Munro, I.C. 1993. Scientific Principles for Evaluating the Potential for Adverse Effects from Chlorinated Organic Chemicals in the Environment. Reg Toxicol Pharmacol 18:313-356.

Nestmann, E.R., and Orr, J.C. 1993. Current Issues in Hazard Assessment: Role of Mutagenicity/Carcinogenicity Mechanisms in Risk Assessment. Presented at National Workshop on the Characterization of Risks to Humans and the Environment, June 21-23, Hull, Québec.

Blakey, D.H., Nestmann, E.R., Bayley, J.M., Maus, K.L., and Douglas, G.R. 1992. Mutagenic Activity of p-Toluenesulfonhydrazide. Toxicol Ind Health 8:369-376.

Ivett, J., Brusick, D., Young, R., Chappel, C.I., and Nestmann, E.R. 1992. Genetic Toxicology Evaluation of Commercial Beers III. Results from *In Vitro* Analyses for SCE, Chromosome Aberrations, and Forward Mutation Assays at the HGRPT Locus, in CHO Cells, Mutat Res 298:43-51.

Brusick, D.J., Jagannath, D.R., Galloway, S.M., and Nestmann, E.R. 1992. Genotoxicity Hazard Assessment of Caramel Colour-III and Colour-IV. Food Chem Tox 30(5):403-410.

Swierenga, S.H.H., Gilman, J.P.W., Brillinger, R.L., and Nestmann, E.R. 1991. Recommended Protocols Based on a Survey of Current Practice in Genotoxicity Testing Laboratories: Study design. Mutat Res 246:227-234.

Swierenga, S.H.H., Bradlaw, J.A., Brillinger, R.L., Gilman, J.P.W., Nestmann, E.R., and San, R.C. 1991. Recommended Protocols Based on a Survey of Current Practice in Genotoxic Testing Laboratories: I. Unscheduled DNA Synthesis Assay in Rat Hepatocyte Cultures. Mutat Res 246:235-254.

Nestmann, E.R., Brillinger, R.L., Gilman, J.P.W., Rudd, C.J., and Swierenga, S.H.H. 1991. Recommended Protocols Based on a Survey of Current Practice in Genotoxicity Testing Laboratories: II. Mutation in Chinese Hamster Ovary, V79 Chinese Hamster Lung and L5178Y Mouse Lymphoma Cells, Mutat Res 246:255-284.

Dunkel, V.C., Rogers, C., Swierenga, S.H.H., Brillinger, R.L., Gilman, J.P.W., and Nestmann, E.R. 1991. Recommended protocols based on a survey of current practice in genotoxicity testing laboratories: III. Cell transformation in C3H/10T1/2 mouse embryo cell, BALB/c 3T3 mouse fibroblast and Syrian hamster embryo cell cultures, Muta Res 246:285-300.

Swierenga, S.H.H., Heddle, J.A., Sigal, E.A., Gilman, J.P.W., Brillinger, R.L., Douglas, G.R., and Nestmann, E.R. 1991. Recommended protocols based on a survey of current practice in genotoxicity testing laboratories: IV. Chromosome aberration and sister chromatid exchange in Chinese hamster ovary, V79 Chinese hamster lung and human lymphocyte cultures. Mutat Res 246:301-322.

Brillinger, R.L., Nestmann, E.R., Sigal, E.A., and Swierenga, S.H.H. 1991. Recommended protocols based on a survey of current practices in genotoxicity testing laboratories: Study evaluation. Mutat Res 246:323-330.

Strauss, H.S., Hattis, D., Franklin, C., and Nestmann, E.R. 1991. A Guide For Compiling Existing Data on Microorganisms Developed for Environmental Release to Assist in Hazard Assessment.

Nestmann, E.R., and Sigal, E.A. 1991. Review of Established Regulatory Policies Using Genotoxicity Tests, Current Capabilities, and Recommendations for Future Development. Prepared for the Ministry of the Environment.

McPherson, M.F., and Nestmann, E.R. 1990. The SIMULTEST approach for testing mutagens in the *Salmonella* microtitre fluctuation assay. Environ Molec Mutag 16:21-25.

000061

Nestmann, E.R., Gowdy, K.M., Lynch, B., and Feniak, A. 1990. Biological Risk Assessm n-Nitrosodimethylamine (NDMA). Prepared for hearings of an Environmental Appeal Board Province of Ontario.

Nestmann, E.R., Treissman, D., Kesicki, L., Munro, I., and Solomon, K. 1990. Effects of Conventional and Organic Farming Methods on Issues of Food Safety and the Environment: Assessment of Natural Toxins and Synthetic Pesticides.

Munro, I.C., Orr, J., and Nestmann, E.R. 1990. The Effect of Tissue Damage on Cancer Production.

Nestmann, E.R., Starodub, M.E., and Sardella, A. 1990. Alternatives to Replace or Reduce the Number of Animals used in Toxicological Testing.

Nestmann, E.R., and Brillinger, R.L. 1989. Genetic toxicology in hazard and risk assessment. Perspectives 7:1-4.

Nestmann, E.R., Brillinger, R., and Trevors, J.T. 1989. Regulatory Procedures and Criteria for Risk Analysis of Products of Biotechnology: Evaluation of Existing Canadian Structure and Recommended Changes to Ensure Plant Protection.

Grice, H.C., Nestmann, E.R., and Brillinger, R. 1989. Toxicological Evaluation and Food Safety Assessment of Allyl Isothiocyanate.

Nestmann, E.R., and Grice, H.G. 1989. Safety of Rubber Additives. Chemical & Engineering News. December 1989. Letter to the Editor.

Munro, I.C., and Nestmann, E.R. 1989. Toxicological Profile of Bismuth Compounds.

Nestmann, E.R., Wilson, R., and Gowdy, K. 1989. Toxicological Risk Assessment for 3-Monochloropropane-1,2-Diol Intake from Normal Dietary Consumption.

Narod, S., Douglas, G.R., Nestmann, E.R., and Blakey, D.H. 1988. Paternal Mutagens: Evidence from paternal exposure? Environ Molec Mutag 10:401-415.

Munro, I.C., Nestmann, E.R., and Rowell, G. 1988. Report on Safety and Efficacy of a Novel Dietary Fibre Source.

Clary, J.J., Nestmann, E.R., and Gowdy, K.M. 1988. Acrylic Acid Risk Assessment.

Willes, R.F., and Nestmann, E.R. 1988. Carcinogenicity/Mutagenicity Workshop.

Clary, J., Munro, I.C., and Nestmann, E.R. 1988. Assessment of the Significance of Benign Tumours in Rats Exposed to Methylene Chloride.

Grice, H.C., Nestmann, E.R., and Brillinger, R. 1988. A Comparison of the Validity of an 18 Month *versus* a 24 Month Duration for Carcinogenicity Bioassays in the B6C3F1 Mouse.

Munro, I.C., and Nestmann, E.R. 1988. Criteria for Assessing the Relevance of Experimental Carcinogenesis Studies to Humans.

Willes, R.F., and Nestmann, E.R. 1988. Development of Criteria for PAH Concentrations in Waste.

Chappel, C.I., McGee, S., Willes, R.F., and Nestmann, E.R. 1988. The Significance to Human Health of the Trace Amounts of Nitrosamine That May Be Present in Beer.

Nestmann, E.R., Brillinger, R.L., McPherson, M.F., and Maus, K.L. 1987. The SIMULTEST: A new approach to screening chemicals with the *Salmonella* reversion assay. Environ Molec Mutag 10:169-181.

Nestmann, E.R., Potter, A.A., and Kowbel, D.J. 1986. Effects of two micrometer (2 um) DNA on survival and mutagenesis in *Saccharomyces cerevisiae*. Can J Genet Cytol 28:154-160.

Kowbel, D.J., Ramaswamy, S., Malaiyandi, M., and Nestmann, E.R. 1986. Mutagenicity studies in *Salmonella*: Residues of ozonated and/or chlorinated water fulvic acids. Environ Mutag 8:253-262.

Potter, A.A., Hanham, A.F., and Nestmann, E.R. 1985. A rapid method for the extraction and purification of DNA from human leukocytes. Cancer Lett 26:335-341.

Nestmann, E.R., Douglas, G.R., Kowbel, D.J., and Harrington, T.R. 1985. Solvent interactions with test compounds and recommendations for testing to avoid artifacts. Environ Mutag 7:163-170.

Nestmann, E.R., and Lee, E.G.-H. 1985. Genetic activity in *Saccharomyces cerevisiae* of compounds found in effluents of pulp and paper mills. Mutat Res 155:53-60.

Potter, A.A., Nestmann, E.R., and Iyer, V.N. 1984. Introduction of the plasmid pKM101-associated muc genes into *Saccharomyces cerevisiae*. Mutat Res 131:197-204.

Nestmann, E.R., Otson, R., Kowbel, D.J., Bothwell, P.D., and Harrington, T.R. 1984. Mutagenicity in a modified Salmonella assay of fabric-protecting products containing 1,1,1-trichloroethane in a modified *Salmonella* assay. Environ Mutagen 6:71-80.

Kowbel, D.J., Malaiyandi, M., Paramsigamani, V., and Nestmann, E.R. 1984. Chlorinated of ozonated soil fulvic acid: Mutagenicity studies in *Salmonella*. Sci Total Environ 37:171-176.

Nestmann, E.R., Kowbel, D.J., Kamra, O.P., and Douglas, G.R. 1984. Reduction of mutagenicity of pulp and paper mill effluent by secondary treatment in an aerated lagoon. Hazardous Waste 1:67-72.

Harrington, T.R., Nestmann, E.R., and Kowbel, D.J. 1983. Suitability of the modified fluctuation assay for evaluating the mutagenicity of unconcentrated drinking water. Mutat Res 120: 97-103.

Potter, A.A., Selvaraj, G., Nestmann, E.R., and Iyer, V.N. 1983. Improved *Salmonella* tester strain carrying a pKM101-derived plasmid. Mutat Res 122:7-12.

Nestmann, E.R., and Lee, E.G.-H. 1983. Mutagenicity of constituents of pulp and paper mill effluent in growing cells of *Saccharomyces cerevisiae*. Mutat Res 119:273-280.

Kamra, O.P., Nestmann, E.R., Douglas, G.R., Kowbel, D.J., and Harrington, T.R. 1983. Genotoxic activity of pulp mill effluent in *Salmonella typhimurium* and *Saccharomyces cerevisiae* assays. Mutat Res 118:269-276.

McKague, A.B., Rettig, S.J., Trotter, J., Douglas, G.R., and Nestmann, E.R. 1983. The chlorination of dihydroconiferyl alcohol. Can J Chem 61:545-549.

Vidoli, R.P., Nestmann, E.R., Kowbel, D.J., and Nasim, A. 1983. Pre-replicative and post-replicative mutagenesis in RAD+ and rad1-1 strains of *Saccharomyces cerevisiae*. Mutat Res 122:39-45.

McPhee, W.J., and Nestmann, E.R. 1983. Predicting potential fungicide resistance in fungal populations using a continuous culturing technique. Phytopathol 73:1230-1233.

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Douglas, G.R., Grant, C.E., Bell, R.D.L., Salamone, M.F., Heddle, J.A., and Nestmann, E.R. 1983. Comparative mammalian *in vitro* and *in vivo* studies on the mutagenic activity of rhodamine WT. Mutat Res 118:117-125.

Nestmann, E.R., Stephen, E.R., Kowbel, D.J., and Nasim, A. 1982. Differential survival as an indicator of potential mutagenicity using repair deficient strains of *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*. Can J Genet Cytol 24:771-775.

Williams, D.T., Nestmann, E.R., LeBel, G.L., Benoit, F., Otson, R., and Lee, E.G.-H. 1982. Determination of mutagenic potential and organic contaminants of Great Lakes drinking water. Chemosphere 11:263-276.

Kowbel, D.J., Nestmann, E.R., Malaiyandi, M., and Helleur, R. 1982. Determination of mutagenic activity in *Salmonella* of residual fulvic acids after ozonation. Water Res 16:1537-1538.

Douglas, G.R., Nestmann, E.R., Grant, C.E., Bell, R.D.L., Wytsma, J.M., and Kowbel, D.J. 1981. Mutagenic activity of Diallate and Triallate determined by a battery of *in vitro* mammalian and microbial tests. Mutat Res 85:45-56.

Nestmann, E.R., Kowbel, D.J., and Wheat, J. 1981. Mutagenicity in *Salmonella* of dyes used by defence personnel for the detection of liquid chemical warfare agents. Carcinogenesis 12:879-883.

Maus, K., Nestmann, E.R., and Kowbel, D.J. 1981. Absence of mutagenicity induced by phloxine and phloxine B in *Salmonella typhimurium* and in *Escherichia coli*. Mutat Res 91:315-320.

Nestmann, E.R., Nasim, A., Haynes, R.H., and Kowbel, D.J. 1981. Genetic activity of actinomycin D in *Saccharomyces cerevisiae* but not in *Escherichia coli*. Mutat Res 89:229-236.

Nestmann, E.R., Otson, R., Williams, D.T., and Kowbel, D.J. 1981. Mutagenicity of paint removers containing dichloromethane. Cancer Lett 11:295-302.

Ruddick, J., Villeneuve, D., Chu, I., Nestmann, E.R., and Miles, D. 1981. An assessment of the teratogenicity in the rat and mutagenicity in *Salmonella* of mono-2-ethylhexyl phthalate. Bull Environ Cont Toxicol 27:181-186.

Nasim, A., Hannan, M., and Nestmann, E.R. 1981. Pure and mosaic clones -- a reflection of differences in mechanisms of mutagenesis by different agents in *Saccharomyces cerevisiae*. Can J Genet Cytol 23:73-79.

Kowbel, D.J., and Nestmann, E.R. 1981. Enhanced sensitivity of the fluctuation assay using a modified incubation procedure. Mutat Res 91:33-36.

Ellenton, J.A., Douglas, G.R., and Nestmann, E.R. 1981. Mutagenic evaluation of 1,1,2,3-tetrachloropropene, a contaminant in pulp mill effluents, using a battery of *in vitro* mammalian and microbial tests. Can J Genet Cytol 23:17-25.

Nestmann, E.R., Lee, E.G.H., Matula, T.I., Douglas, G.R., and Mueller, J.C. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents, using the *Salmonella*/mammalian-microsome assay. Mutat Res 79:203-212.

Chu, I., Villeneuve, D., Nestmann, E.R., Douglas, G.R., and Becking, G.C. 1980. The subacute toxicity and mutagenicity of cis-9,10- epoxystearic acid. Bull Environ Cont Toxicol 25:400-403.

Nestmann, E.R., Kowbel, D.J., and Ellenton, J.A. 1980. Mutagenicity in *Salmonella* of fluorescent dye tablets used in water tracing. Water Res 14:901-902.

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Nestmann, E.R., Chu, I., and Kowbel, D.J. 1980. Short-lived mutagen in *Salmonella* produced by reaction of trichloroacetic acid and dimethyl sulphoxide. Can J Genet Cytol 22:35-40.

Nestmann, E.R., Lee, E.G.H., Mueller, J.C., and Douglas, G.R. 1979. Mutagenicity of resin acids identified in pulp and paper mill effluents using the *Salmonella*/mammalian-microsome assay. Environ Mutag 1:361-369.

Nestmann, E.R., and Kowbel, D.J. 1979. Mutagenicity in *Salmonella* of rhodamine WT, a dye used in environmental water tracing studies. Mutat Res 68:389-392.

Nestmann, E.R., Douglas, G.R., Matula, T.I., Grant, C.E., and Kowbel, D.J. 1979. Mutagenic activity of rhodamine dyes and their impurities as detected by mutation induction in *Salmonella* and DNA damage in Chinese hamster ovary cells. Cancer Res 39:4412-4417.

Nestmann, E.R., LeBel, G.L., Williams, D.T., and Kowbel, D.J. 1979. Mutagenicity of organic extracts from Canadian drinking water in the *Salmonella* mammalian-microsome assay. Environ Mutag 1:337-345.

Nestmann, E.R., Matula, T.I., Douglas, G.R., Bora, K.C., and Kowbel, D.J. 1979. Detection of the mutagenic activity of lead chromate using a battery of microbial tests. Mutat Res 66:357-365.

Nestmann, E.R. 1979. Reduction of sensitivity to ultraviolet light in excision-deficient *Escherichia coli* strain WP2 uvrA-. Can J Genet Cytol 21:95-100.

Nestmann, E.R. 1979. Lethal zygosis in recombination-deficient mutants of *Escherichia coli.* Can J Genet Cytol 12:213-221.

Nestmann, E.R. 1978. Mapping by transduction of mutator gene mutH in *Escherichia coli.* Mutat Res 49:421-423.

Nestmann, E.R. 1977. Antimutagenic effects of spermine and guanosine in continuous cultures of *Escherichia coli* mutator strain mutH. Molec Gen Genet 152:109-110.

Nestmann, E.R. 1975. Mutagenesis by nitrosoguanidine, ethyl methanesulfonate, and mutator gene mutH in continuous cultures of *Escherichia coli.* Mutat Res 28:323-330.

Nestmann, E.R., and Hill, R.F. 1973. Mutagenesis by mutator gene mutHI in continuous cultures of *Escherichia coli.* J Bacteriol 119:33-35.

Hill, R.F., and Nestmann, E.R. 1973. Effect of the recC gene in *Escherichia coli* on frequency of ultraviolet induced mutants. Mutat Res 17:27-36.

Invited Articles, Books, Chapters

Nestmann, E.R., Munro, I.C., Willes, R.F., and Orr, J. 1992. Risk Assessment: An Overview. In: Canadian Environmental Directory 1992, pp. 13-16.

Broekhoven, L.H., and Nestmann, E.R. 1991. Statistical Analysis of the Salmonella Mutagenicity Assay. In: Krewski, D., and Franklin, C.A. (Eds.), Statistics in Toxicology, Gordon and Breach, pp. 205-264.

Huck, P.M., Kellendonk, D., Daignault, S.A., Anderson, W.B., Noot, D.K., Rodger, C.E., Harris, D.I., Savage, E., von Borstel, R., Williams, D.T., and Nestmann, E.R. 1987. Pilot Scale Investigation of Alternative Drinking Water Treatment Processes at Edmonton, Alberta. In: Huck, P.M., and Toft, P. (Eds.) Treatment of Drinking Water for Organic Contaminants, Pergamon Press, New York, pp. 241-261.

Claxton, L.D., Allen, J., Auletta, A., Mortelmans, K., Nestmann, E.R., and Zeiger, E. 1987. Guide for the Salmonella typhimurium/mammalian microsome tests for bacterial mutagenicity. Mutat Res 189:83-91.

Malaiyandi, M., Kowbel, D.J., and Nestmann, E.R., Das, B.S. 1987. Mutagenicity Testing and Determination of Polynuclear Aromatic Hydrocarbons and Nitroaromatics in Photocopier Toners, Exposed Papers and Ambient Air. In: Cooke, M., and Denis, A.J. (Eds.), Polynuclear Aromatic Hydrocarbons: A Decade of Progress, Batelle Press, pp. 557-580.

Franklin, C.A., Nestmann, E.R., and Ritter, L. 1987. Biotechnology: Risk Assessment and Regulation of Genetically Engineered Products. In: LeBaron, H.M., Mumma, R.O., Honeycutt, R.C., and Duesing, J.H. (Eds.), Biotechnology in Agricultural Chemistry, ACS Symposium Series 334, American Chemical Society, Washington, DC, pp. 336-351.

Nestmann, E.R. 1986. A Mutagen is a Mutagen, Not Necessarily a Carcinogen. In: Shankel, D.M., Hartman, P.E., Kada, T., and Hollaender, A. (Eds.), Mechanisms of Antimutagenesis and Anticarcinogenesis, Plenum Press, pp. 423-424.

Douglas, G.R., Nestmann, E.R., and LeBel, G.L. 1986. Contribution of chlorination to the mutagenic activity of drinking water extracts in *Salmonella* and Chinese hamster ovary cells. Environ Health Persp 69:81-88.

Nestmann, E.R. 1985. Biological Methods of Detecting Hazardous Substances. In: Moo-Young, M., Robinson, C.W., and Howell, J.A. (Eds.), Comprehensive Biotechnology, Vol. 4, Pergamon Press, Oxford, pp. 447-466.

Parry, J.M., Arni, P., Brooks, T., Carere, A., Ferguson, L., and Heinisch, J., Inge Vechtomov, S., Loprieno, N., Nestmann, E.R., and von Borstel, R. 1985. Summary Report on the Performance of the Yeast and Aspergillus Assays. In: Ashby, J., de Serres, F.J., Draper, M., Ishidate, M., Margolin, B.H., Matter, B.E., and Shelby, M.D. (Eds.), Evaluation of Short-Term Tests for Carcinogens, Progress in Mutation Research, Vol. 5, Elsevier Science Publishers, pp. 25-46.

Harrington, T.R., and Nestmann, E.R. 1985. Mutagenicity of five compounds in growing cells of haploid yeast strain XV185-14C. Ibid 257-260.

Nestmann, E.R. 1985. Detection of Genetic Activity in Effluents from Pulp and Paper Mills: Mutagenicity in *Saccharomyces cerevisiae*. In: Zimmermann, F.K., and Taylor-Mayer, R.E. (Eds.), Mutagenicity Testing in Environmental Pollution Control, Ellis Harwood, Chichester, pp. 118-125.

Douglas, G.R., Nestmann, E.R., McKague, A.B., San, R.H.C., Lee, E.G.-H., Liu-Lee, V.W., and Kowbel, D.J. 1985. Determination of Potential Hazard From Pulp and Paper Mills: Mutagenicity and Chemical Analysis. In: Stich, H.F. (Ed.), Carcinogens and Mutagens in the Environment, Vol. IV. The Workplace, CRC Press, pp. 151-164.

Douglas, G.R., Nestmann, E.R., McKague, A.B., Kamra, O.P., Lee, E.G.-H., Ellenton, J.A., Bell, R., Kowbel, D., Liu, V., and Pooley, J. 1983. Mutagenicity of Pulp and Paper Mill Effluent: A Comprehensive Study of Complex Mixtures. In: Waters, M., Sandhu, S., Claxton, L., Lewtas, J., Nesnow, S., and Chernoff, N. (Eds.), Applications of Short-Term Bioassays in the Analysis of Complex Environmental Mixtures. Vol. III, Plenum Press, pp. 431-460.

Nestmann, E.R. 1983. Mutagenic Activity of Drinking Water. In: Stich, H.F. (Ed.), Carcinogens and Mutagens in the Environment. Vol. III., Naturally Occurring Compounds. CRC Press, Inc., pp. 137 147.

Nestmann, E.R., Otson, R., LeBel, G.L., Williams, D.T., Lee, E.G.-H., and Biggs, D. 1983. Correlation of Water Quality Parameters with Mutagenicity of Drinking Water Extracts. In: Jolley, R.L., Cumming, R.B., and Brungs, W.A. (Eds.), Water Chlorination: Health Effects and Environmental Impact., Vol. 4, pp. 1151-1164.

Nestmann, E.R. 1982. Studies of Drinking Water Mutagenicity. In: 1982 Annual Report of the International Joint Commission's Committee on the Assessment of Human Health Effects of Great Lakes Water Quality, pp. 13-16.

Nestmann, E.R., and Douglas, G.R. 1981. New Tools for Assessing Mutagenic and Carcinogenic Risk of Municipal and Industrial Wastewaters. In: Moo-Young, M., Robinson, C.W. (Eds.), Advanced Biotechnology. Vol. II, Pergamon Press, pp. 649-658.

Douglas, G.R., Nestmann, E.R., Betts, J., Mueller, J., Lee, E.G.-H., Stich, H.F., San, R.H.C., Brouzes, R., Chmelauskas, A., Paavila, H., and Walden, C. 1980. Mutagenic Activity in Pulp Mill Effluents. In: Jolley, R.L., Cumming, R.B., and Brungs, W. (Eds.), Water Chlorination: Environmental Impact and Health Effects, Vol. II, pp. 865-880.

Nestmann, E.R., and Hill, R.F. 1973. Population changes in continuously growing mutator cultures of *Escherichia coli*. Genet. (Suppl.), 73:41-44.

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CURRICULUM VITAE
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BORN:

CITIZENSHIP: Naturalized U.S. Citizen, 1966

PERSONAL:

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EDUCATION: Washington and Jefferson College,
Washington, Pa. B.A. 1963; Magna Cum Laude

University of Pittsburgh School of Medicine,
Pittsburgh, Pa. M.D., 1967

SUBSEQUENT TRAINING AND POSITIONS;

1967-1969 Intern and Resident in Pathology, Department of Pathology, Massachusetts General Hospital and Instructor in Pathology, Harvard University Medical School, Boston, Massachusetts.

1969-1971 Staff Associate, National Cancer Institute, Experimental Pathology Branch, Chemical Carcinogen Screening Unit, Bethesda, Maryland.

1971-1972 Visiting Scientist, Wenner-Gren Institute, Department of Cell Physiology, Stockholm, Sweden.

1971-1975 Assistant Professor, Department of Pathology, and Member, Fels Research Institute, Temple University School of Medicine, Philadelphia, Pennsylvania.

1975-1979 Chief, Division of Experimental Pathology, American Health Foundation; and Research Associate Professor, Department of Pathology, New York Medical College, Valhalla, New York.

1979-1980 Chief, Division of Pathology and Toxicology, American Health Foundation; and Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.

1980-1987	Associate Director and Chief, Division of Pathology and Toxicology, American Health Foundation; Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1987-1997	Director of Medical Sciences and Chief, Division of Pathology and Toxicology, American Health Foundation; Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1997-1998	Director, Naylor Dana Institute and Chief, Division of Pathology and Toxicology, American Health Foundation; Research Professor, Department of Pathology, New York Medical College, Valhalla, New York; Visiting Lecturer, Graduate School of Health Sciences, New York Medical College, Valhalla, New York.
1999 - present	Professor of Pathology, Department of Pathology, Director of Environmental Pathology and Toxicology, Head, Program on Medicine, Food and Chemical Safety, New York Medical College, Valhalla, New York; Affiliated Faculty, Graduate School of Health Sciences, New York Medical College, Valhalla, New York.

CERTIFICATIONS:

1974	American Board of Pathology
1975	Physician, State Education Department, State of New York
1981	American Board of Toxicology, Recertified, 2002.
1984	Expert in Toxicology, Ministere des Affaires Sociales et de la Solidarite Nationale, Direction de la pharmacie et du medicament, Republic Francais
2000	Fellow in Toxicologic Pathology, International Academy of Toxicologic Pathology

AWARDS AND HONORS:

1963	Phi Beta Kappa, Washington and Jefferson College

1967	Sheard-Sandford Award, American Society of Clinical Pathologists
1967	Alpha Omega Alpha, University of Pittsburgh School of Medicine
1971	Research Training Fellowship, International Agency for Research on Cancer
1980	Association of University Pathologists
1981	Invited Contributor, Special Issue Food and Cosmetics Toxicology, 9:557, 1981, dedicated to Leon Goldberg
1982	Arnold J. Lehman Award, Society of Toxicology
1984	Invited Contributor Hommage au Professeur Rene Truhaut
1987	Citation Classics: Cancer Lett. 1:231, 1976 and Cancer Res. 37:1845, 1977. Institute for Scientific Information, Current Contents, Vol. 30, No.36, September 7, 1987
1988	Citation Classics: In Vitro 12:521, 1976; 12:821, 1976; 13:809, 1977, 14:824, 1978. Institute for Scientific Information. Current Contents, Vol. 32, No. 9, February 27, 1989
1989	Featured on cover of Cancer Research, Volume 49, November 1
1995	Featured on cover of Cancer Research, Volume 55, April 15
1996	Awards Lecture, Society of Toxicology
1997	Invited Contributor, Special Issue Cancer Letters, 118:1, 1997, dedicated to Phillipe Shubik
1998	Top 10 Most Frequently Cited Articles in 25 years of Toxicologic Pathology Toxicologic Pathology 10:3-10, 1982; Toxicologic Pathology 26:452, 1998
2001	Ambassador in Toxicology Award, Mid-Atlantic Chapter of the Society of Toxicology.
2002	Enhancement of Animal Welfare Award, Society of Toxicology.

RECOGNITION:

1996-01	Who's Who in American/50th-56th Editions
1996-00	Who's Who in the East/26-28th Editions
1996-03	Who's Who in Science and Engineering/3rd-6th Editions
1997/1998	American Men and Women of Science Directory of American Research & Technology
1998-00	Official American Board of Medical Specialties Directory of Board Certified Medical Specialists 30th-33rd Editions

SOCIETIES:

1974	American Association for Cancer Research
1978	Society of Toxicology
1981	Society of Toxicologic Pathologists
1991	International Society of Regulatory Toxicology and Pharmacology

EDITORIAL RESPONSIBILITIES:

1980	Co-Editor, Differentiation and Carcinogenesis in Liver Cell Cultures. Vol. 349. New York Academy of Sciences.
1980-1981	Consulting Reviewer, Oncology Overviews, International Cancer Research Data Bank.
1980-1986	Reviewing Editor, In Vitro.
1980	Co-editor, The Predictive Value of In Vitro Short-term Screening Tests in Carcinogenicity Evaluation. Elsevier/North Holland Biomedical Press.
1981-1983	Editorial Board, Fundamental and Applied Toxicology.
1981-1989	Editorial Board, Toxicology and Applied Pharmacology.

1981-1999	Editorial Board, Nutrition and Cancer.
1981	Meeting Report: Carcinogenesis and Gene Expression in Liver Cultures. Cancer Research 42:2462-2464, 1982.
1982	Consulting Reviewer, Oncology Overview, International Cancer Research Data Bank Program, National Cancer Institute.
1982-1993	Editorial Board, Mutation Research, Genetic Toxicology Testing Section.
1983	Co-Editor, Colon Carcinogenesis. CRC Press.
1983	Co-Editor, Cellular Systems for Toxicity Testing. Vol. 407. New York Academy of Sciences.
1983	Co-Editor, Tests Courts de Cancerogenese/Short-term Tests for Carcinogenesis, Elsevier Science Publishers BV, Amsterdam.
1983-1992	Editorial Board, Chemico-Biological Interactions.
1983-1996	Editorial Board, Toxicologic Pathology.
1984-present	Founding Editor, Cell Biology and Toxicology.
1987	Meeting Report: Causative and Modifying Factors in Digestive Tract Cancer. Cancer Research 47:922-923, 1987
1988-present	Editorial Board, Archives of Toxicology
1988	Editor, Sweeteners: Health Effects, Princeton Scientific Publishing Company.
1989	Editorial Board, Complex Mixtures and Cancer Risk, IARC Scientific Publications, International Agency for Research on Cancer
1990	Meeting Report: American Health Foundation 20th Anniversary International Symposium on Causes and Prevention of Cancer. Preventive Medicine, in 20:534-547, 1991
1991-present	International Advisory Board, European Journal of Cancer Prevention
1992	Proceedings of the Second International Conference on Longevity and

Aging: Environmental and Nutritional Influences on Aging and Cancer Experimental Gerontology, Volume 27, Special Issue, 1992

1993 Editor-in-Chief, Antioxidants Chemical, Physiological, Nutritional and Toxicological Aspects, Princeton Scientific Publish. Co.

1994-present Area Editor for Carcinogenesis, Drug and Chemical Toxicology.

1997 Co-Editor, Reducing Dietary Fat: Putting Theory into Practice, Journal of The American Dietetic Association, Volume 97, Supplement 1, 1997

2001 Co-Editor, Toxicology, Special Issue, Volume 166, Number 3, Festschrift J.H. Weisburger.

MEETINGS ORGANIZED:

1980 Conference on Differentiation and Carcinogenesis in Liver Cell Cultures. New York Academy of Sciences. New York, NY.

1980 Workshop on the Predictive Value of in vitro Short Term Screening Tests in the Evaluation of Carcinogenicity. Scientific Council of the Netherlands Cancer Society. Dalen, The Netherlands.

1982 Quo Vadis Symposium on Short Term Tests in Carcinogenesis and Mutagenesis. Research Center Clin-Midy. Montpellier, France.

1983 Conference on Carcinogenesis and Gene Expression in Liver Cultures United States-Japan Cooperative Cancer Research Program. Honolulu, Hawaii.

1984 Conference on Cellular Systems for Toxicity Testing, New York Academy of Sciences, New York, NY.

1986 Conference on Causative and Modulating Factors for Digestive Tract Cancer United States-Japan Cooperative Cancer Research Program. Tokyo, Japan.

1986 International Conference on Cancer Research. Theories of Carcinogenesis. The Norwegian Cancer Society, Oslo, Norway.

1986 Conference on Non-Mutagenic Carcinogens: How Much Risk to Man? The Robens Institute, University of Surrey, Guildford, England.

1987 Conference on Sweeteners: Health Effects. American Health Foundation,

New York.

1987 International Symposium in Genetic Toxicology, National Science Foundation (U.S.) and Council of Scientific and Industrial Research (India), University of Calcutta, Calcutta, India.

1988 International Symposium on Causes and Prevention of Cancer, American Health Foundation in cooperation with American Cancer Society and National Cancer Institute, New York, NY.

1989 International Conference on Environmental and Nutritional Influences on Aging and Cancer, American Health Foundation in cooperation with National Institute on Aging, New York, NY.

1990 Conference on Cancer Prevention for Black Americans, Metropolitan Life Insurance, Company, New York, NY.

1991 International Conference on Antioxidants: Chemical, Physiological, Nutritional and Toxicological Aspects, American Health Foundation, Tarrytown, NY.

1991 Second International Conference on Theories of Carcinogenesis. Norwegian Cancer Society, Oslo, Norway.

1992 1st International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.

1993 2nd International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.

1993 American Health Foundation, 25th Anniversary Conference and Celebration, Toward Optimal Health: Examining Goals for Nutrition and the Environment, Tarrytown, NY.

1994 3rd International Course on the Safety Assessment of Pharmaceuticals, Tarrytown, NY.

1995 International Congress on Hepatocytes-Applications in Cell Biology, Toxicology and Medicine, Tubingen, Germany.

1996 Conference, Reducing Dietary Fat: Putting Theory Into Practice, American Health Foundation, New York, NY.

1996	4th International Course on the Safety Assessment of Pharmaceuticals, Part I, White Plains, NY.
1996	4th International Course on the Safety Assessment of Pharmaceuticals, Part II, San Francisco, CA.
1997	5th International Course on the Safety Assessment of Medicines, Part I, White Plains, NY.
1998	6th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2000	7th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2001	8th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2002	International Symposium on Antimutagenesis and Anticarcinogenesis, New York Medical College, Valhalla, NY

NATIONAL AND INTERNATIONAL RESPONSIBILITIES

1975	Consultant, Pesticides, Toxic Substance and Solid Waste Management, United States Environmental Protection Agency.
1975-1978	Member, Epidemiology Committee, Breast Cancer Task Force, NationalCancer Institute.
1976-1977	Member, Program Committee, American Association for Cancer Research.
1976	Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man: Some Miscellaneous Pharmaceutical Substances, International Agency for Research on Cancer.
1976-1978	Co-Chairperson, Subcommittee on Rat Liver Tumors, Committee on Histologic Classification of Laboratory Animal Tumors, Institute of Laboratory Animal Resources, National Research Council.
1977-1978	Member, Panel on Kepone/Mirex, Scientific and Technical Assessments of Environmental Pollutants, Environmental Studies Board, Commission Natural Resources, National Research Council.

1979-1980	Member, Panel on Unscheduled DNA Synthesis, Gene-Tox Program, U.S. Environmental Protection Agency.
1980-1981	Member, Panel of Experts Associated with Technical Report Review Subcommittee, National Toxicology Program, Department of Health and Human Services.
1980	Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man-Antineoplastic and Immunosuppressive Drugs, International Agency for Research on Cancer.
1980-1986	Panel of Reviewers, Netherlands Cancer Foundation.
1981	Advisor, Technical Committee, Society of Toxicology.
1981-1982	Member, Task Group on the Differentiation Between Genotoxic and Epigenetic Carcinogens, International Commission on Protection Against Environmental Mutagens and Carcinogens.
1982	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Chemicals and Industrial Processes Associated with Cancer in Humans, IARC Monographs Volumes 1 to 29, International Agency for Research on Cancer.
1982-1983	Consultant, Office of Health and Environmental Assessment, Reproductive Effects Assessment Group, U.S. Environmental Protection Agency.
1982-1983	Member, International Expert Committee to the Nutrition Foundation on the Relevance of Mouse Liver as a Model for Assessing Carcinogenic Risk, Nutrition Foundation, Incorporated.
1982-1983	Coordinator, Assays of DNA Damage, Collaborative Study on Short-Term Tests for Genotoxicity and Carcinogenicity. International Programme on Chemical Safety, World Health Organization.
1983	Member, Working Group on the Mechanisms of Chemical Carcinogenesis, International Agency for Research on Cancer.

1983-1984	Member, Expert Committee on Pathology/Toxicology and Expert Committee on Short-Term Testing, International Life Sciences Institute.
1984-1987	Assessor, National Health and Medical Research Council Panel of Independent Assessors, National Health and Medical Research Council, Commonwealth of Australia.
1984-1985	Member, Committee on the Carcinogenicity of Cyclamates, Food and Nutrition Board, Commission on Life Sciences, National Research Council.
1984-1985	Member, Task Group of DNA Repair, Subcommittee on Genetic Toxicology, American Society for Testing and Materials.
1985-1987	Member, Toxicology Study Section, National Institutes of Health.
1985	Vice-Chairman, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Naturally Occurring Substances, Food Additives and Amino Acid Pyrolysates in Food, International Agency for Research on Cancer.
1985-1986	Member, Awards Committee, Society of Toxicology.
1986	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42, International Agency for Research on Cancer.
1987	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, International Agency for Research on Cancer.
1988	Participant, Tox-90s Conference, Society of Toxicology.
1989	Organizing Committee, Workshop on the Effects of pesticides on Human Health, Task Force on Environmental Cancer and Heart and Lung Disease.
1989	Chairman, Working Group and Chairman, Subgroup on Animal

	Carcinogenicity, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Humans: Some Pharmaceutical Drugs, International Agency for Research on Cancer.
1989	Participant and Member of Editorial Board, Workshop on Complex Mixtures and Cancer Risk, International Agency for Research and Cancer.
1989	Participant, Working Group on Short-Term In Vitro and In Vivo Tests, Workshop on Research to Improve Predictions of Long-Term Chemical Toxicity, National Research Council.
1990-present	Member, Committee of Education on Toxicologic Pathology, International Federation of Societies of Toxicologic Pathologists.
1991	Member, Working Group on Approaches to Classifying Carcinogens According to Mechanisms of Action, International Agency for Research on Cancer.
1992-1993	Member, Expert Panel on Interpretive Review of the Potential Adverse Effects of Chlorinated Organic Chemicals on Human Health and the Environment, CanTox, Inc.
1993-1999	Member, Committee on Evaluation of the Research Program "Cancer Risk Factors and Prevention," German Cancer Center.
1993-present	Member, Board of Trustees, International Life Sciences Institute, Health and Environmental Sciences Institute. Chair, Membership Development Committee, 2002.
1993-1999	Member, Cellular Telephone Advisory Committee, Harvard Center for Risk Analysis, Harvard School of Public Health.
1993-1999	Wireless Technology Research Peer Review Board.
1993-present	Member, Subcommittee on Carcinogenicity, International Federation of Societies of Toxicologic Pathologists.
1995-1998	Member, International Committee on Wireless Communication Health Research (ICWCHR).
1995-1997	Member, Committee on Research Opportunities and Priorities for EPA,

	Commission on Geosciences, Environment, and Resources, National Research Council.
1996	Reviewer, U.S. Environmental Protection Agency (EPA), PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures.
1996	Participant, Developmental Planning for Office of Dietary Supplements (ODS), National Institutes of Health.
1996-1997	Member, Advisory Board to the Calcium Channel Blockers/Cancer Study, Boston University School of Medicine, Slone Epidemiology Unit.
1997	Member, Working Group on Short/Medium Term Carcinogenicity Tests and Genetic and Related Effects. International Agency for Research on Cancer.
1998	Member, Working Group - Re-evaluation of Some Industrial Chemicals. International Agency for Research on Cancer.
1999-present	Member, Subcommittee on Upper Limits, Committee on Reference Levels of Nutrients, National Academy of Sciences, Institute of Medicine.
1999	Member, Working Group on Predictive Value of Gastric Neuroendocrine Tumours and Forestomach Tumours in Rodents for Carcinogenic Hazard Identification. Co-Chairperson, Forestomach Tumors. International Agency for Research on Cancer.
2000	Member and Report Coordinator, Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel. U.S. Environmental Protection Agency.
2001	Reviewer, Office of Dietary Supplements, National Institutes of Health. Annual Bibliography of Significant Advances in Dietary Supplement Research - 2000.
2001-present	Member, Accreditation Committee, International Academy of Toxicologic Pathology.
2002	Peer Review Member, U.S. Environmental Protection Agency "Perchlorate Environmental Contamination: Toxicological Review and Risk

Assessment."

2002 WHO Temporary Adviser, 59th Meeting of the Joint Expert Committee on Food Additives (JECFA).

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SUBMISSION END